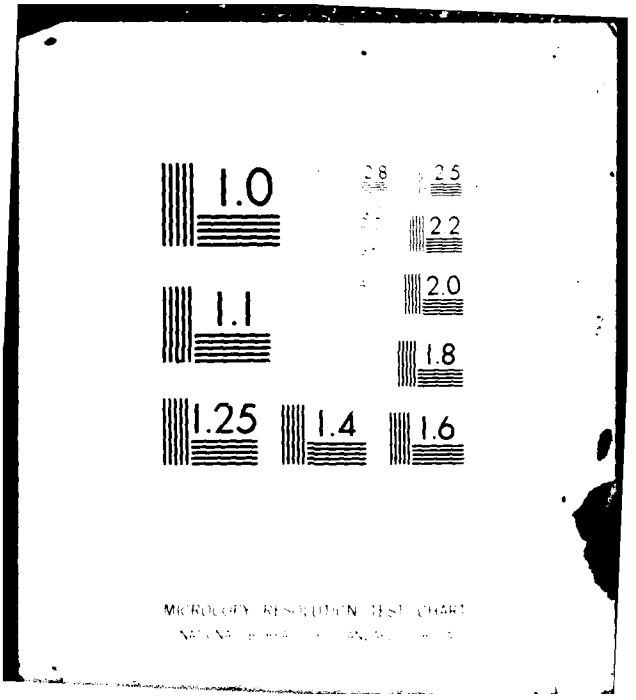
AD-A117 391 STATE UNIV OF NEW YORK AT ALBANY RESEARCH FOUNDATION F/G 6/15
ASSESSMENT OF NEUROLOGICAL EFFECTS OF DRUGS ON OCULOMOTOR AND V--ETC(U)
FEB 82 E G KEATING DAAK11-79-C-0027
UNCLASSIFIED NL


1.0
2.8
2.5
2.2
1.1
2.0
1.8
1.25
1.4
1.6

(10)

February 28, 1982

Commander
U.S.A. Biomedical Laboratory
Attn: SGRD-UV-RB Behavioral Toxicology Branch
Aberdeen Proving Ground, Maryland 21010

Final Report:

DAAK 11-79-C-0027

Assessment of Neurological Effects of Drugs on Oculomotor and Visual Function in the Primate

Submitted by,

E. Gregory Keating, Ph.D.
Professor of Anatomy
and Neurology

The opinions or assertions contained herein are the private views of the author and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

TABLE OF CONTENTS

FIGURES AND TABLES

Figures

Tables

INTRODUCTION

Background and Military Significance. The principal sources of neurotoxicity in both the military and industrial setting are agents that specifically affect cholinergic transmission in the nervous system. Of these the most potent threat comes from the class of irreversible cholinesterase inhibitors, the organophosphate compounds. Their effect is to produce an excessive and prolonged build-up of acetycholine at central and peripheral synapses by inhibiting the enzyme which normally catalyzes the hydrolysis of acetycholine to choline and acetic acid. The pharmacological strategies to counter the effects of the anticholinesterases involve: 1, attempts to reactivate acetylcholinesterase after it is inhibited, (e.g. with oximes such as 2PAM-chloride and TMB4); 2, advance protection of the enzyme from the inhibitor, e.g., by prophylactic binding with a reversible inhibitor such as physostigmine; or 3, reducing the effects of acetylcholine build-up with anticholinergic drugs such as atropine and benactyzine.

The maneuvers themselves affect neural transmission in cholinergic portions of the nervous system and therefore come with their own risks. They do in fact have widespread effects on behavior (for review, see Longo, 1966; Brimblecombe, 1974; Levin & Rodnitzky, 1976; Duffy et al, 1979). In general the cholinesterase inhibitors in high doses produce respiratory failure and death. At lower levels of exposure widespread desynchronization of the EEG, fatigue, difficulty in concentration, visual hallucinations, incoordination, oculomotor imbalance, muscle weakness, tremor, amnesia, and reduced rates of learning have been reported. The effects of anticholinergic agents such as the naturally occurring alkaloids like atropine and synthetic anticholinergics are no less global: loss of power of concentration, drowsiness, ataxia, mydriasis, loss of the ability to carry out complex or sequential movements, and emotional lability. The neurotoxicity of enxyme reactivator drugs such as the oximes (2-PAM-Cl, TMB_4) is less known. Transient blurred vision and diplopia have been described (Sidell & Groff, 1971) probably caused by altered transmission of the neuromuscular junction. They may have some central nervous system effects (Lipp & Dola, 1980).

Lacking in the literature is a knowledge of the more subtle neurotoxicity of these pharmacological maneuvers. At lower doses that provide effective therapy they may have no gross neurological side effects but still drastically disrupt performance of military personnel engaged in complex operations with sophisticated equipment. The research program carried out under the aegis of the Behavioral Toxicology Branch of the Biomedical Laboratory is concerned with developing behavioral tests that are sensitive to subtle toxic chemical insult but that are also valid animal models of behaviors required of military personnel in the field.

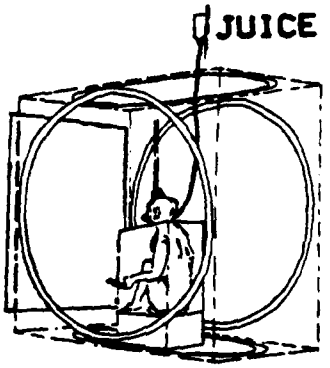
The primary purpose of the project reported here was to develop a test for monkeys that captured the visual, oculomotor, and cognitive capabilities analogous to those required of field personnel engaged in searching for hidden targets. The result was the Visual Search test described below. This report details the experiments which measured the effects of several cholino-specific agents (atropine, benactyzine, TMB_4, physostigmine & TAB) on the visual and oculomotor competence of rhesus monkeys engaged in visual search.

METHODS

Five adolescent rhesus monkeys (M. mulatta) served as subjects. They were housed and cared for by the Animal Care Facility at Upstate Medical Center.* On testing days the monkeys were water-deprived and kept at 90% of their normal weight (5-8 K), and on these days all of their liquid intake was achieved as reward in the testing apparatus.

Recording of Eye Movements. Eye movements were recorded with the magnetic search coil technique (Fuchs & Robinson, 1966). The monkey sat in a primate restraining chair positioned so that its eyes were centered in a double magnetic field. The field was produced by voltages in four large coils of wire surrounding the monkey (Figure 1). A small coil of wire was surgically

Figure 1



implanted around the optic globe of one eye of the animal and leads from the coil were brought up from the orbit under the scalp to an electrical connector atop the monkey's head. Rotations of the eye coil in the magnetic field induced a voltage that is a linear function of the rotation of the eye. A phase detector separated the voltages induced by horizontal and vertical eye movements. Since eye and head movements are indistinguishable the head was held rigid by a holder attached with bolts and dental acrylic to the monkey's skull.

* The experiments reported here were conducted according to The Guide for Care & Use of Laboratory Animals (1978) as prepared by the Committee on Care & Use of Laboratory Animals, National Research Council, DHEW Publication No. (NIH) 78-23.

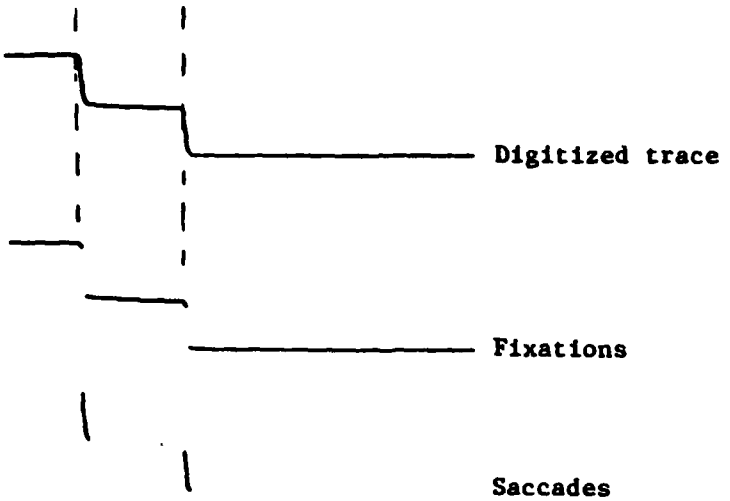


Figure 2

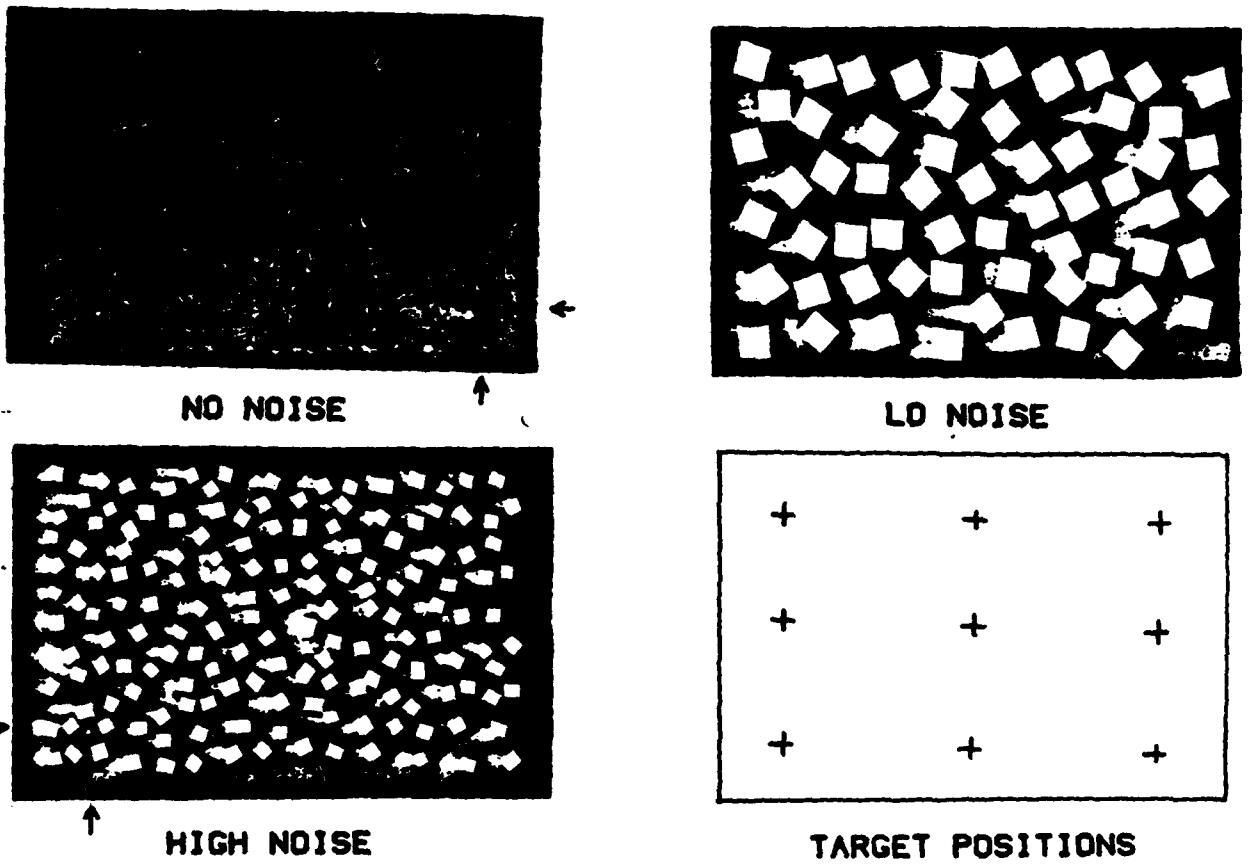
Saccadic Gaze Shift
Horizontal channel

The horizontal and vertical eye movement signals were sampled every millisecond by a microprocessor. The computer first separated the saccadic movements of the eyes from the fixations by a duration and velocity criterion. (See Appendix for details.) A movement exceeding 10 deg/sec was judged to be a saccadic shift of gaze. Any slower epoch that lasted for at least 100 msec was named a fixation. Figure 2 demonstrates the algorithm. At the top of the Figure is a digitized but otherwise unanalyzed trace taken from the horizontal channel. It contains 3 fixations and two saccadic shifts. The lower traces are the portions of this trace recognized as saccades or as fixations by the computer.

The monkey faced a 4' square projection screen. A borderless rectangular area in the center of the screen subtending 22^{o} x 36^{o} of visual angle was used as the viewing area. An optical bench projected stimuli onto the screen from behind. First, the monkey learned to press a lever to make a small white spot appear on the screen. It then learned to fixate the spot steadily and wait for it to dim unpredictably for 0.5 seconds. If the monkey released the lever during the dimming period and only then, it received a squirt of orangeade delivered to its mouth. The dimming was subtle enough to require the monkey to foveate the spot to reliably see the event. Thus, the spot which could be moved anywhere within the viewing area served during calibration to entrain the monkey's gaze to a known location. During formal testing, the spot could be embedded in an array of distractors and serve as the target to be found in a visual search task.

Visual Search Test. Figure 3 shows the stimuli employed in the Visual Search Test. When the monkey initiated a trial, shutters in front of two projectors opened simultaneously. One presented the target which could appear on a trial at any one of the locations marked by crosses in the figure. The target position was shifted between trials by mirror galvanometers. The second projector presented the distractor elements (noise) projected from 35 mm slides. During the formal testing, the stimuli went off. If the monkey released the lever during the dim period, it was rewarded and the next trial was enabled following a 0.7 sec. delay. If the monkey released the lever

Figure 3



too early or late, a 1.2 second delay was imposed. The computer judged a target to have been acquired if a fixation fell within a 3° radius of the target. In plotting the position of the fixation relative to the target the entire system had a typical inaccuracy $\pm$ 0.5° with a worst case inaccuracy of 2.0°.

For the Visual Search test the target could appear under one of three conditions of varying difficulty. The NO NOISE condition was easiest; the target appeared alone on an otherwise blank screen. In the LO NOISE and HIGH NOISE condition the target was embedded in textures of background distractors that made it harder to find. A daily testing run included 40-50 calibration trials and two sessions of Visual Search testing. Each session contained one block each of the NO, LO, and HIGH NOISE condition. A block contained 36 trials. Each week the monkey underwent three days in a row of such testing which established a baseline that was compared to performance on the fifth day when the monkey received an injection of the drug of interest. The baseline/drug sequence was repeated on the following week using a different dose of the same drug.

Drug Protocol

Monkeys were tested on the doses and administration schedule of atropine, benactyzine, TMB_4, physostigmine, or TAB schedule shown in subsequent tables. Each dose and a saline control injection was tested twice and the entire dose sequence required

8-10 weeks of testing. When the monkey completed the sequence with one drug, it was started on a new schedule with a different agent. Drugs were administered by intramuscular injection into the lateral thigh.

On atropine trials the animal was injected, immediately placed in the testing apparatus and the eye position apparatus was calibrated. Formal testing of the Visual Search test began 45 minutes (t.45) after injection. Half of the data was collected from t.45-70, called the EARLY session, and was followed by a 15 minute pause. The second, LATE session, was run during the period from t.75-90.

Trials for the other 4 drugs were run in a similar pattern except that the EARLY session was run at t.15-30 and the LATE session at t.45-60.

MEASURES

Neurological Symptoms: At the start and end of the EARLY and LATE sessions we observed the monkeys for obvious neurological effects. The testing apparatus constrained the monkey's movement but pupillary diameter, vomiting, tremor, ptosis, and jaw weakness could be observed. Limb weakness evident when the monkey transferred to and from the test apparatus was recorded.

Oculomotor Competence: A polygraph provided a written record of the raw horizontal and vertical eye movement signals collected during the session. In addition, the computer quantified certain parameters of eye movements. Some of them require definition:

Fixation - an epoch in which velocity of movement remained below 10^{o}/sec for at least 100 msec.

Saccade - an epoch in which velocity of movement exceeded 10^{o}/sec for at least 4 msec.

Fixation drift - failure to hold a point of gaze. Specifically the distance traversed during the course of a fixation (expressed in minutes of arc) = 60 arctan x/y, where x = distance across screen, y = distance of screen from monkey.

Fixation duration - average duration of all fixations made during a trial (in msec.).

On-target fixation - any fixation falling within a 3^{o} radius of the target.

Targeting error - the radial distance from the target of the first fixation to fall within the on-target sector (in minutes of arc).

Saccadic velocity - average velocity of all saccades made prior to fixating the target (in degrees of arc).

Saccadic duration - average duration of all saccades (in msec).

Reaction time - time elapsed between stimulus onset and the beginning of the first saccade.

In decribing drug effects on eye movements typical examples have been reported in the format, e.g., (fixation drift: 48 vs. 16 $\pm$ 8) where 16 $\pm$ 8 minutes of visual angle represents the normal average and standard deviation of baseline performance against which a drugged value of 48' is being compared.

Measures of Visual Search: Three indices were chosen to describe the monkeys' success in Visual Search:

1. Percent of trials in which the target was successfully fixated.

2. On successful trials, the time required to find the target, i.e. time elapsed between stimulus onset and the first fixation to fall within 3° of the target.

3. On successful trials, the numbers of fixations required to foveate the target.

The raw scores from each of 108 trials for a session were averaged to yield a session score for each of these measures. Thus the performance on the No, Low and High conditions were collapsed into a single score. The effects of drugs on the measures were expressed as Z scores or standard units of deviation of the drug from the baseline session scores:

$$Z = \frac{\bar{X}_D - \mu_B}{\sigma_B}$$

where μ_B = average of the baseline sessions for a given drug (N = 20-30)

$\bar{X}_D$ = average session score for the drug day

σ_B = standard deviation of the baseline sessions.

Early drug sessions were compared to Early baseline sessions, and Late drug to Late baseline sessions.

Finally, to supplement the Z scores and provide some feeling for the absolute magnitude of effects, a "worst case" table is given of session scores from the drug session showing the severest decrement in performance.

RESULTS

Baseline Performance

Table 1 lists scores averaged over 20 baseline sessions of the Visual Search Test for one subject. They are typical of the other subjects and indicate that the monkeys achieved a consistent high level of baseline performance.

Table 1. Baseline Performance of Subject 4 During Atropine Testing

	Baseline Average	Baseline Std. Dev.
Percent of successful trials	97.5	2.0
Reaction time to begin search (msec)	234	15.6
Time to find target (msec)	316.2	23.3
Number of fixations to find target	1.24	.11
Oculomotor:		
Fixation drift (min.)	21	3.9
Fixation duration	815.8	81.2
Targeting error (min.)	28.0	5.24
Saccadic velocity (deg/sec)	219	17.5

The small standard deviation indicated a consistent level of performance over the 20-30 baseline days during a 10 week course of testing several doses of a single drug. Repeated trials with several drugs tested over the course of a year or more did not appear to degrade the monkeys' baseline performance (Figure 4).

To control for conditioning to the injection procedure alone the monkeys were injected with saline once each week on one of the baseline days according to an unpredictable schedule. Comparison of these to other baseline scores revealed no difference in performance (discussed further below).

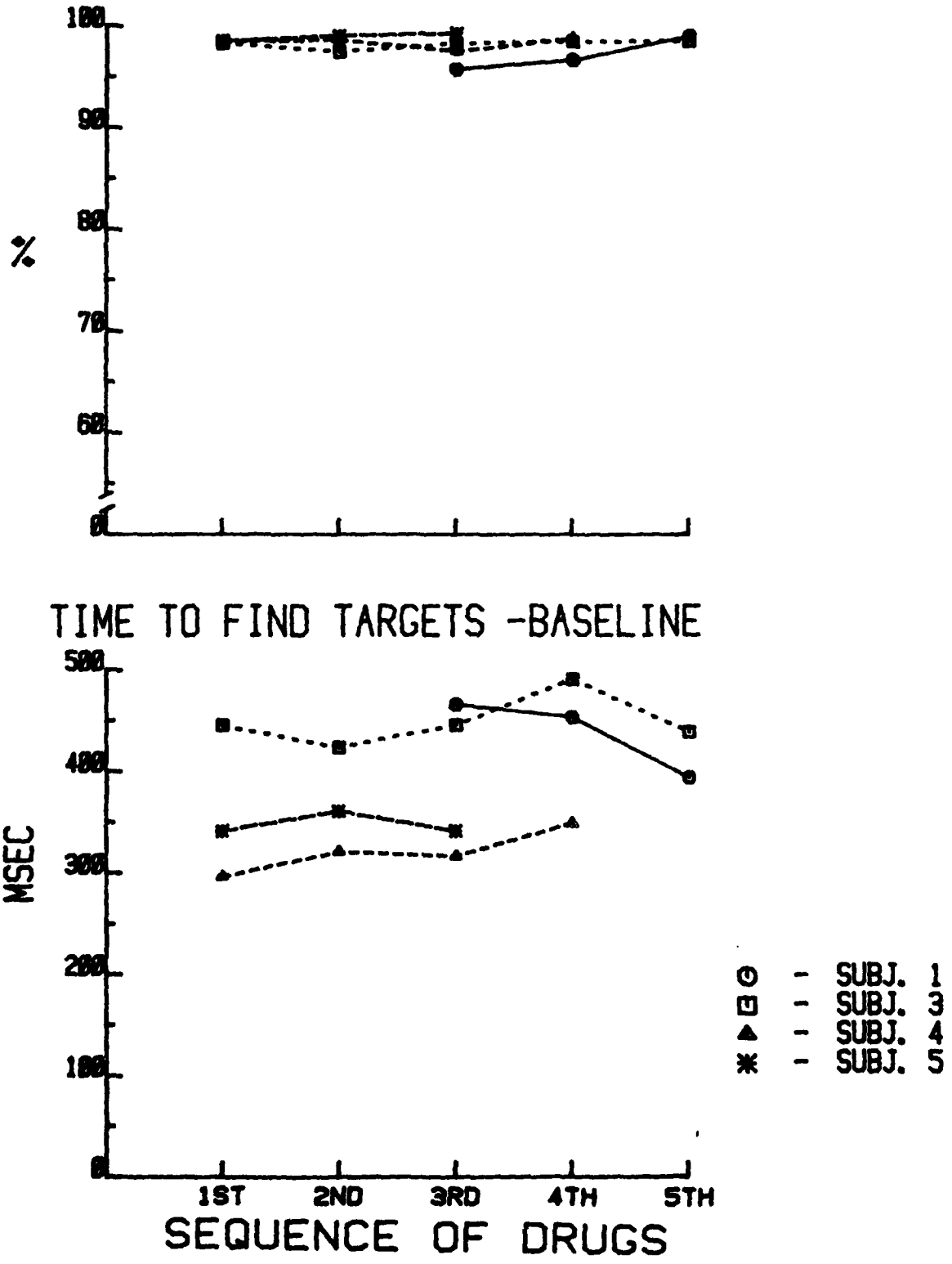


Figure 4. Baseline performance on two measures of Visual Search over a sequence of several drugs, shown from first to the last drug tested on that subject.

Drug Effects

The monkeys received the drugs according to the following sequence:

Table 2. Sequence of Drug Testing For Each Subject

	1st	2nd	3rd	4th	5th
Subj. 1	Atr	Ben	TMB	Phy	TAB
Subj. 2	Ben	Atr			
Subj. 3	TMB	Ben	Atr	Phy	TAB
Subj. 4	Ben	TMB	Atr	TAB	
Subj. 5	Atr	Ben	TAB		

ATROPINE

Table 3. Schedule of Completed Drug Trials

Doses: A = .014 mg/K; B = .045; C = .14; C+ = .25;
d = Saline; E = .44

Subject 1	C	A	A	D	C	B	B	D	E	E		
	x	x	x	x	*	x	x	x	*	*		
Subject 2$	A	C	B	B	A	C	D	D	E	E		
	x	*	x	x	#	-terminated-						
Subject 3	A	C	B	B	A	C	D	D	E	E	C+	C+
	c	c	c	c	c	c	c	c	*	*	c	*
Subject 5	A	B	B	C	D	A	C	D	C+	C+		
	c	c	c	c	c	c	c	c	c	c		
Subject 4	D	D	A	B	A	B	C	C	C+	C+		
	c	c	c	c	c	c	c	c	c	c		

x = trial completed; data analyzed manually
c = trial completed; data analyzed by computer
* = monkey refused to test
# = data rejected for technical reasons
$ = atropine data from subject 2 is not reported. Data became too erratic as headholder loosened and finally fell off.

.014 mg/K

Neurological Symptoms: No obvious symptoms.

Oculomotor Competence: Normal.

Visual Search: Normal.

.045 mg/K

Neurological Symptoms: Slight mydriasis appeared consistently but no other symptoms were noted.

Oculomotor Competence: Normal, except for increase in spiking pulses occurring in the vertical channel.

Visual Search: A decrement in the number of fixated
argets appeared inconsistently in 2 subjects. However,
erformance on successful trials was competent. The reaction
ime to begin search, the time, and the number of fixations
o find the target were normal.

14 mg/K

Neurological Symptoms: Consistent mydriasis widened the
upil to 6-7 mm (4.5-5.0 is normal for these lighting conditions).
he mydriasis lasted with but slight improvement for the 1.5 hours
f testing. No muscle weakness was evident.

Oculomotor Competence: The record revealed fixations
ractured into shorter segments by small transients in the
ignal. Drifting of fixations and slowed, rounded saccades
ccurred. These changes appeared in the calculated oculomotor
arameters as excessive fixation drift (31 vs. 20 ± 4.7 minutes)
n the Early session and in the Late session as fixation drift,
horter fixation durations (517 vs. 764 ± 99 msec), and slower
accadic velocities (268 vs. 294 ± 11.4 deg/sec).

Visual Search: The Z scores (in the following graphs)
veraged for the monkeys as a group revealed a deficit expressed
s a lowered percent of successful trials and an increase in
he time required to find the target. The graphs of individual
onkeys' performance indicate that the deficit was inconsistent
nd in some cases fairly small.

25 mg/K

Neurological Symptoms: Severe mydriasis persisted through
he entire testing period. In some cases mild muscle weakness
as evident as a hanging jaw and some effort at postural support
hen the monkey transferred cages. Obvious ptosis did not appear
ut the monkey s tended to close their eyes when not actively
earching for targets. Muscle weakness when observed appeared
nly during the Late session.

Oculomotor Competence: The polygraph recorded a frequent
ailure to hold a fixation. The computer algorithm sometimes
nterpreted the meandering gaze as excessive drift of fixations
52 vs. 26 ± 9.8 minutes) or alternatively, as prolonged saccades
33 vs. 26 ± 2 msec). These calculated parameters probably
epresent the eye movements at their best. The polygraph shows
he meandering to worsen in the interval between trials when
he eye signals were not sampled by the computer.

Visual Search: One subject (3) refused to test during the Late session the first day it received this dose and refused again during both Early and Late session on the second drug test. The other subjects tested intermittently. They at times would not initiate trials, but did attempt to find the target if the experimenter triggered the stimuli for them.

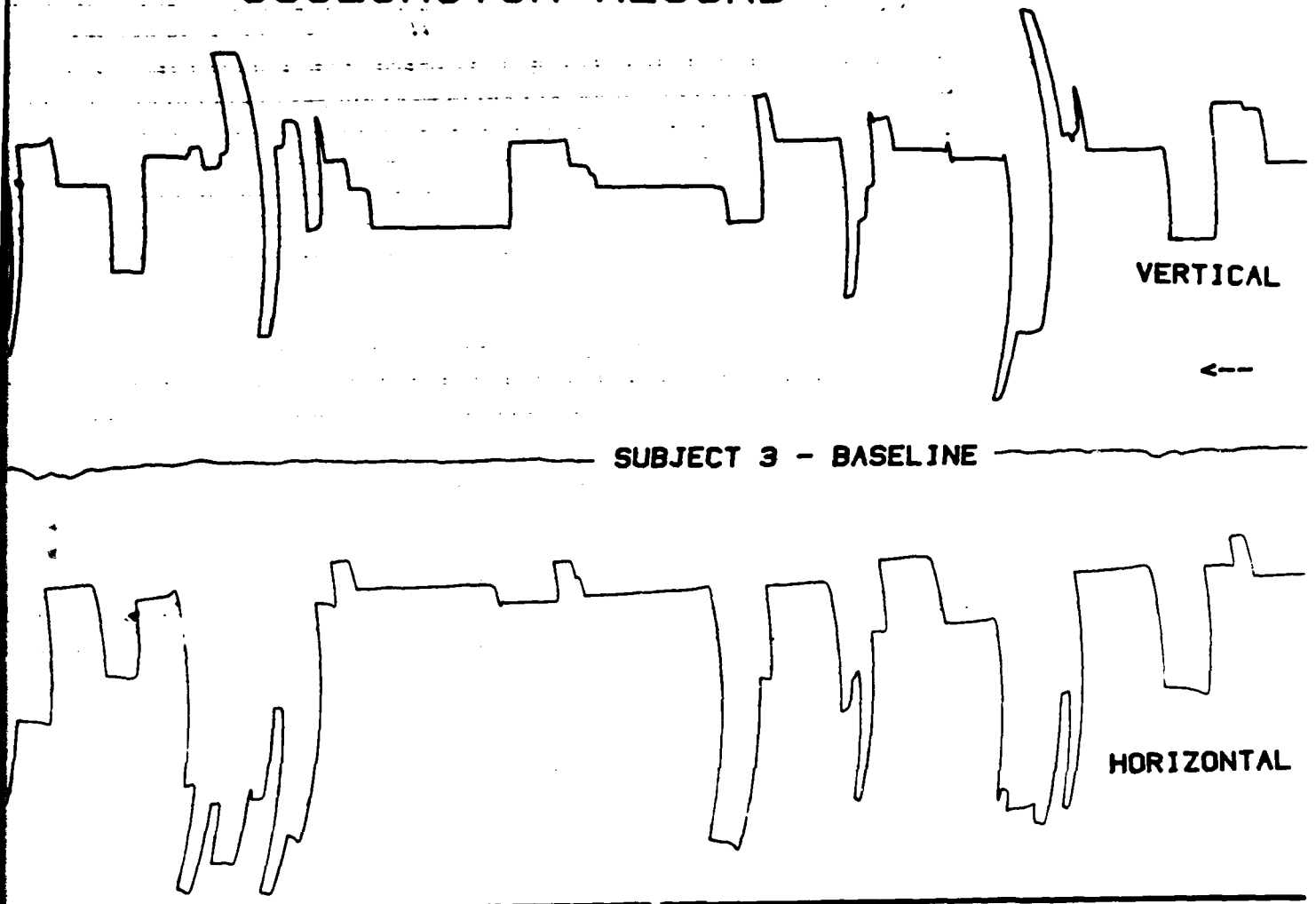
As a group the monkeys found the target less often than normal (the worst case is shown in Table 4). On successful trials they were slower by 200 msec in fixating the target. The reaction time to begin search was close to normal as was the length of the scan path needed to acquire the target.

.45 mg/K

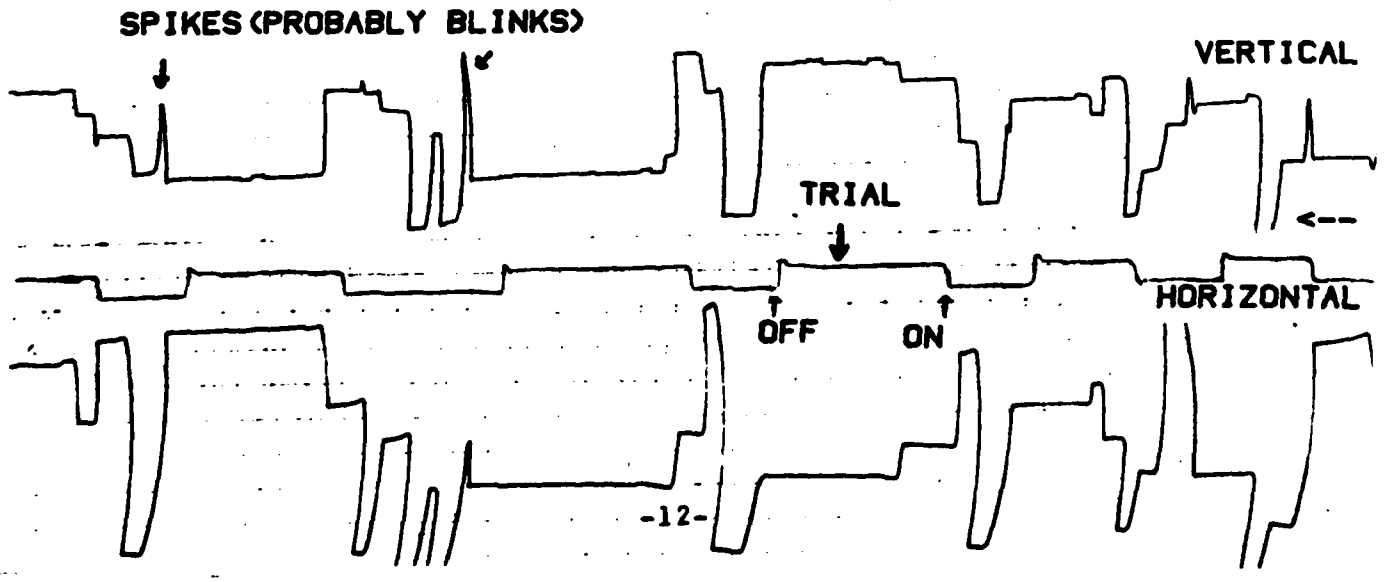
Two subjects (1, 3) who were tested at this dose both refused to perform the Search test for up to two hours after injection. Their neurological status differed little from the effects at .25 mg/K and was characterized by severe mydriasis and mild trunk and limb weakness. Due to its disruptive effects on Search, in subsequent monkeys this dose was replaced in the protocol with the lesser dose of .25 mg/K.

Figure 5

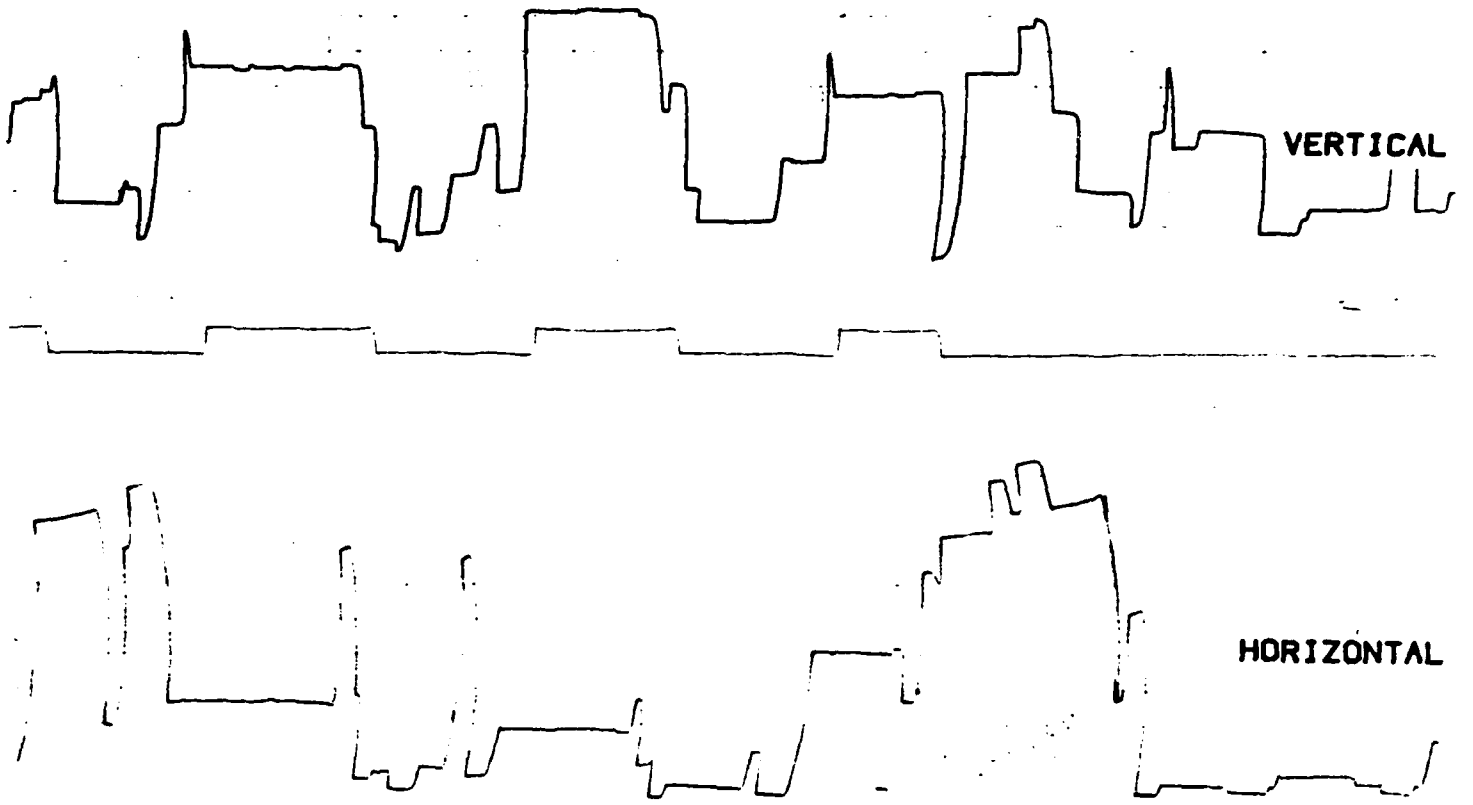
OCULOMOTOR RECORD - ATROPINE



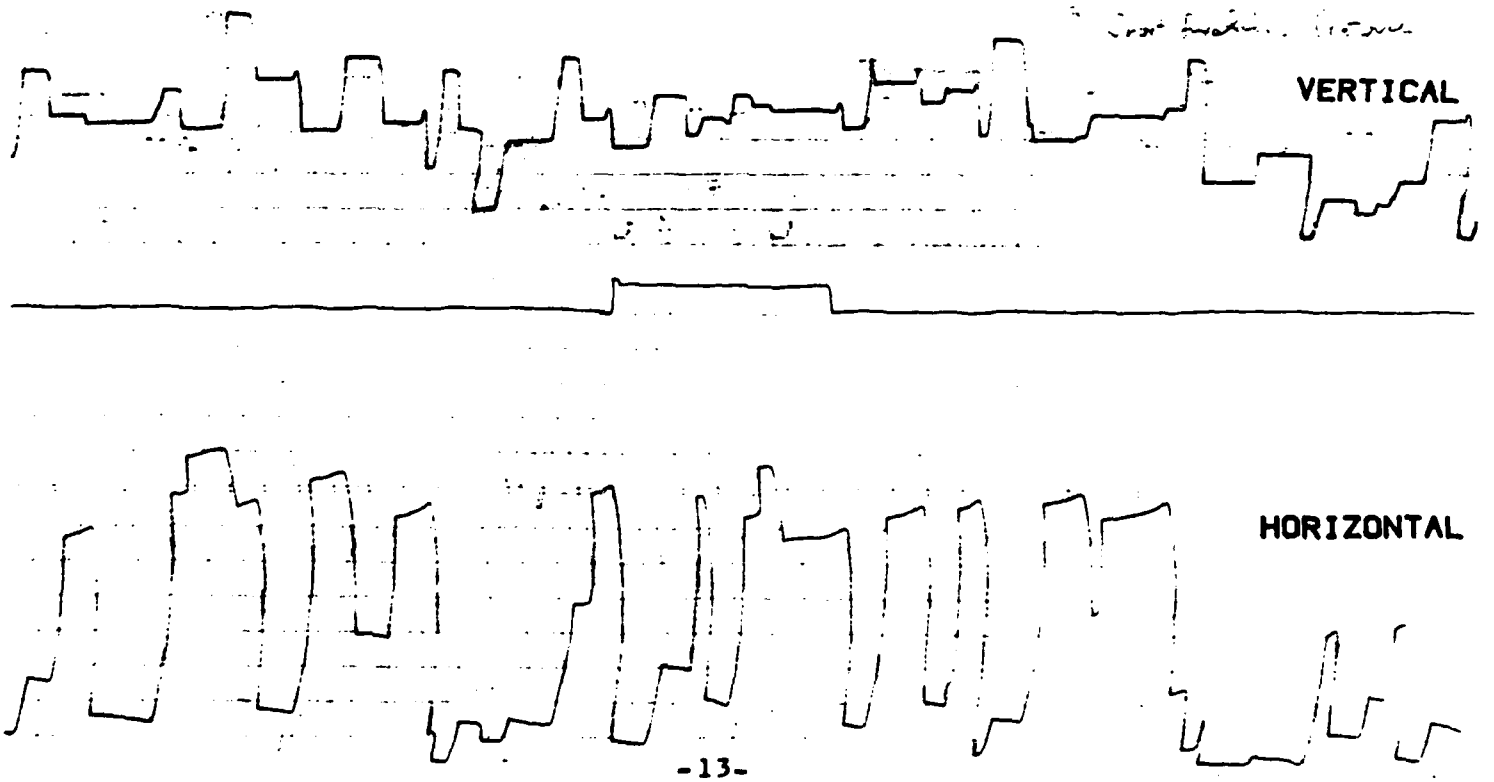
SUBJECT 3 - ATROPINE - .014 MG/K



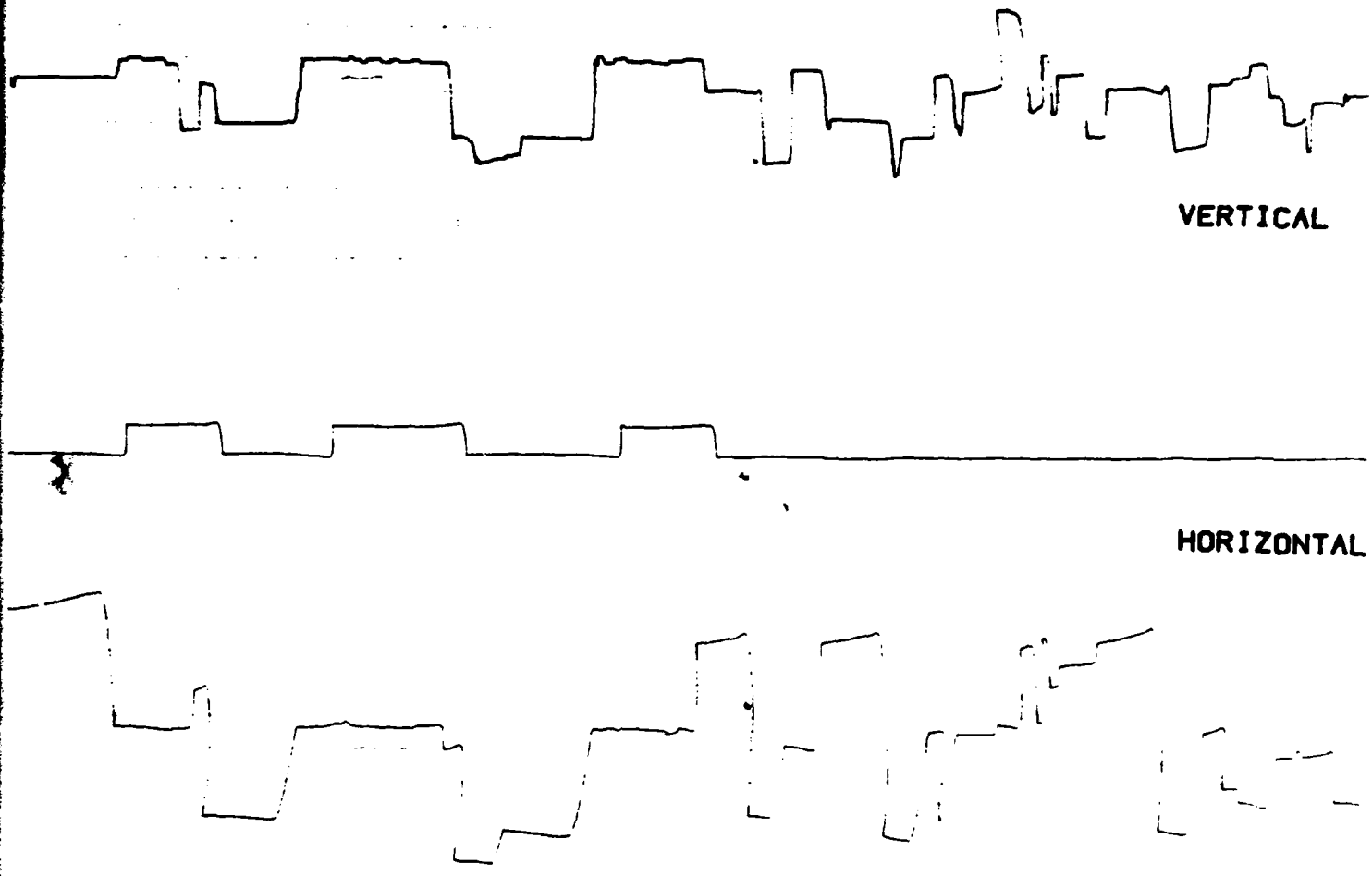
SUBJECT 3 - ATROPINE - .14 MG/K

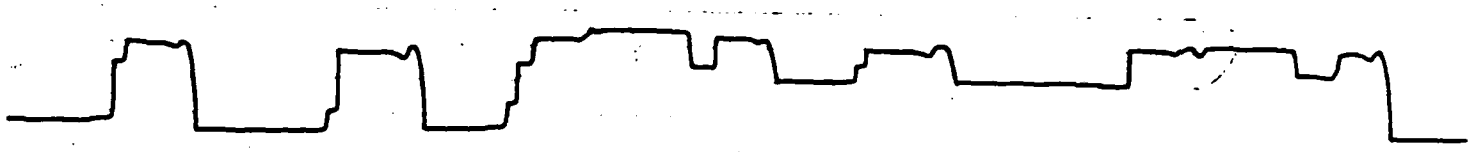


SUBJECT 3 - ATROPINE - .25 MG/K



SUBJECT 3 - ATROPINE - .45 MG/K





VERTICAL

SUBJECT 4 - BASELINE

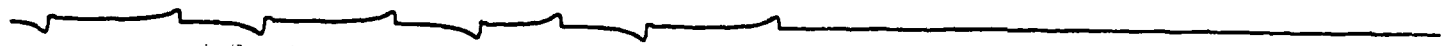
HORIZONTAL

SUBJECT 4 - ATROPINE - .045 MG/K

SPIKES

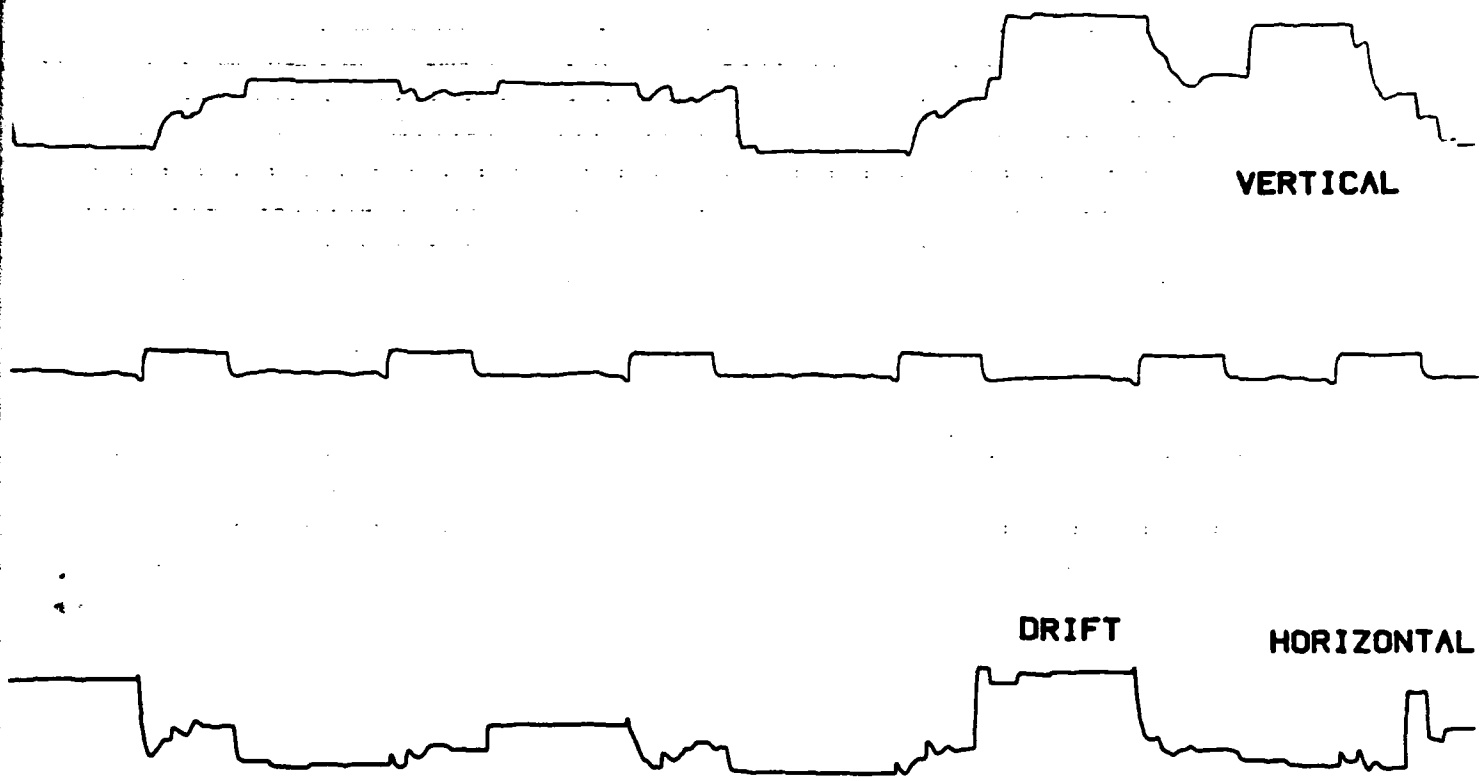
VERTICAL

(PROBABLY BLINKS)

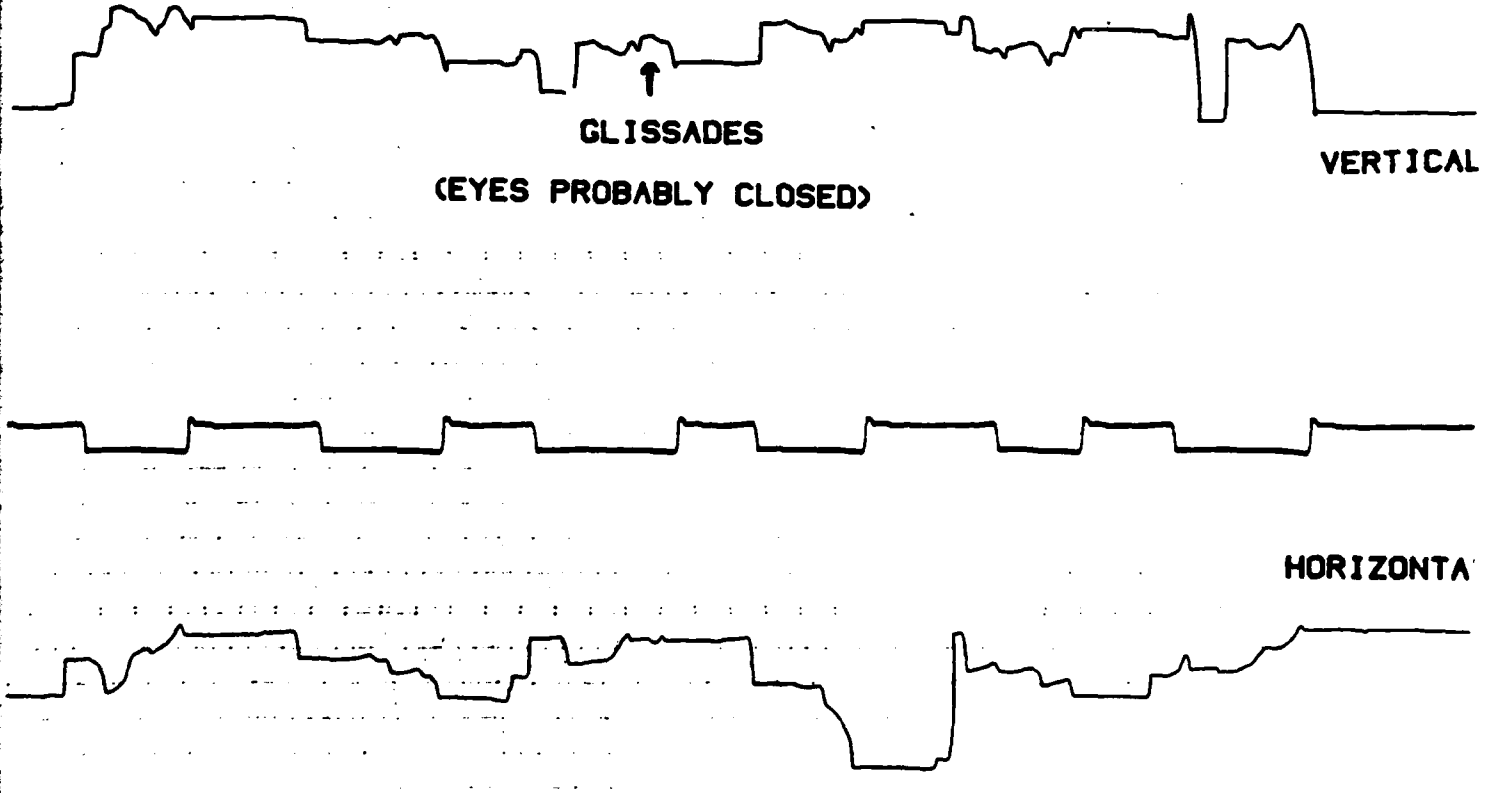


HORIZONTAL

SUBJECT 4 - ATROPINE - .14 MG/K

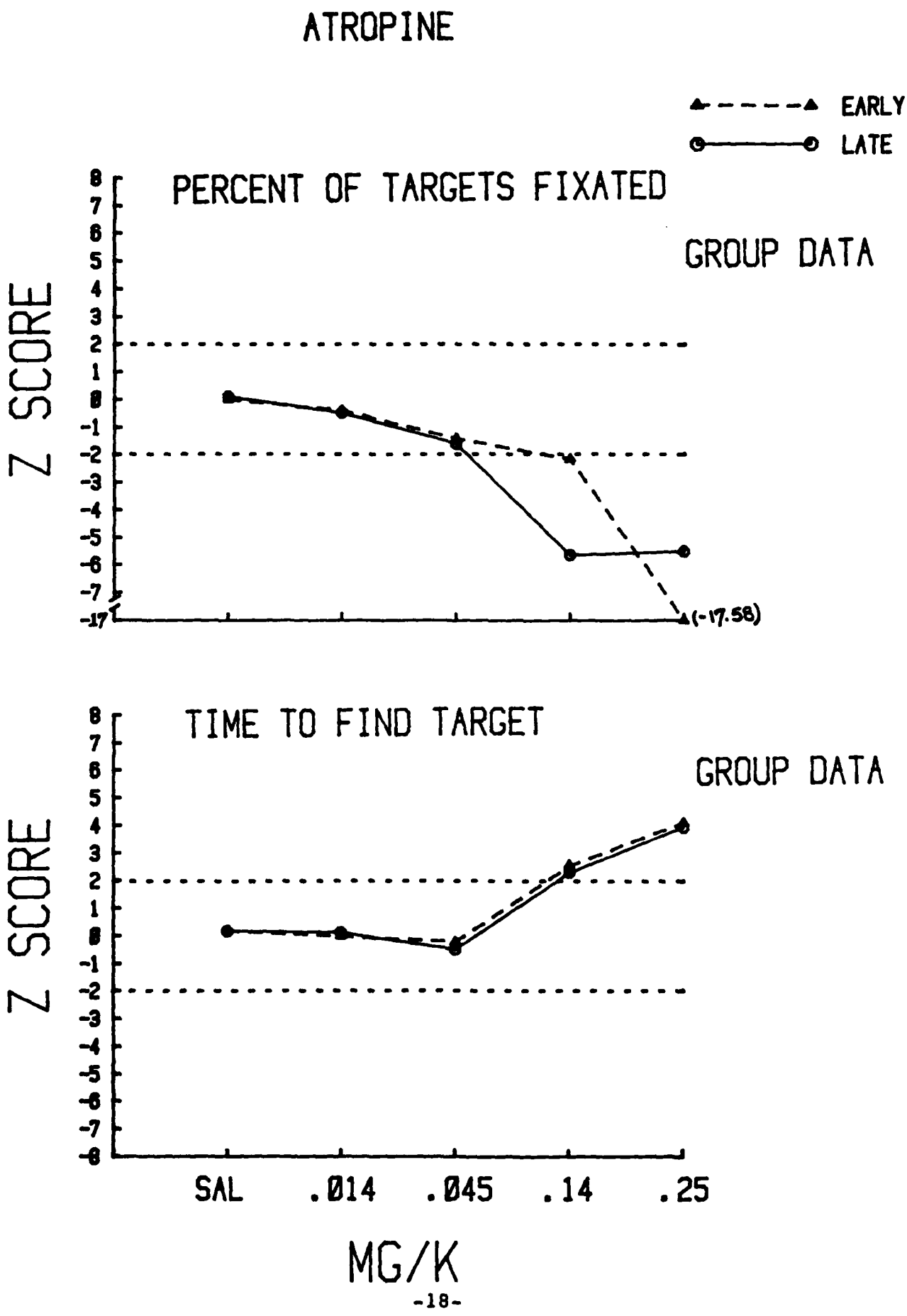


SUBJECT 4 - ATROPINE - .25 MG/K



Legend for Graphs: The area between the dashed lines represents tolerance limits within which the monkey's performance is defined as not differing from normal ($p = .95$; $x = .05$, under the assumption that baseline session scores distribute normally). In all the graphs, the sign of the measure is appropriate, e.g. -z = fewer trials fixated; +z = more time required to fixate the target, etc.

Figure 6


ATROPINE
EARLY
LATE
PERCENT OF TARGETS FIXATED
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-17
(-17.58)
TIME TO FIND TARGET
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.25
MG/K

ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

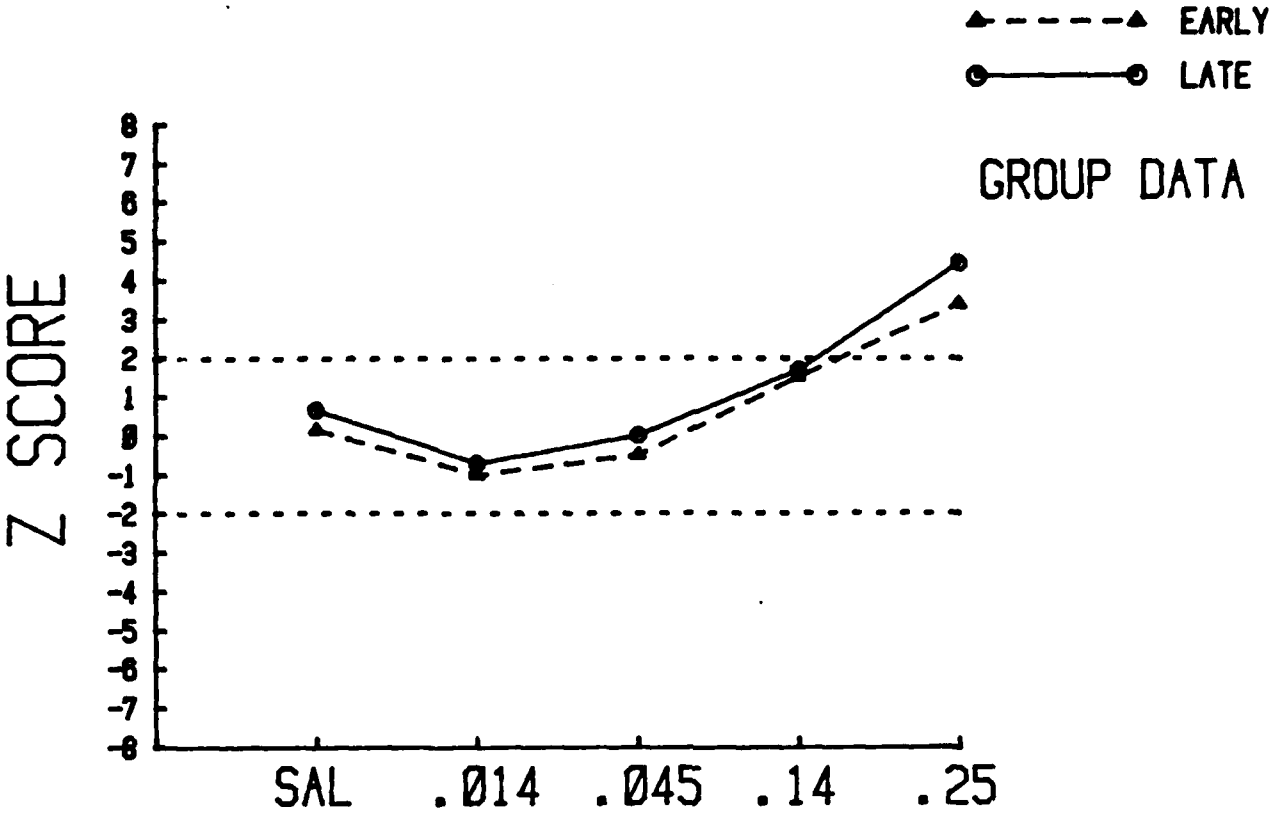
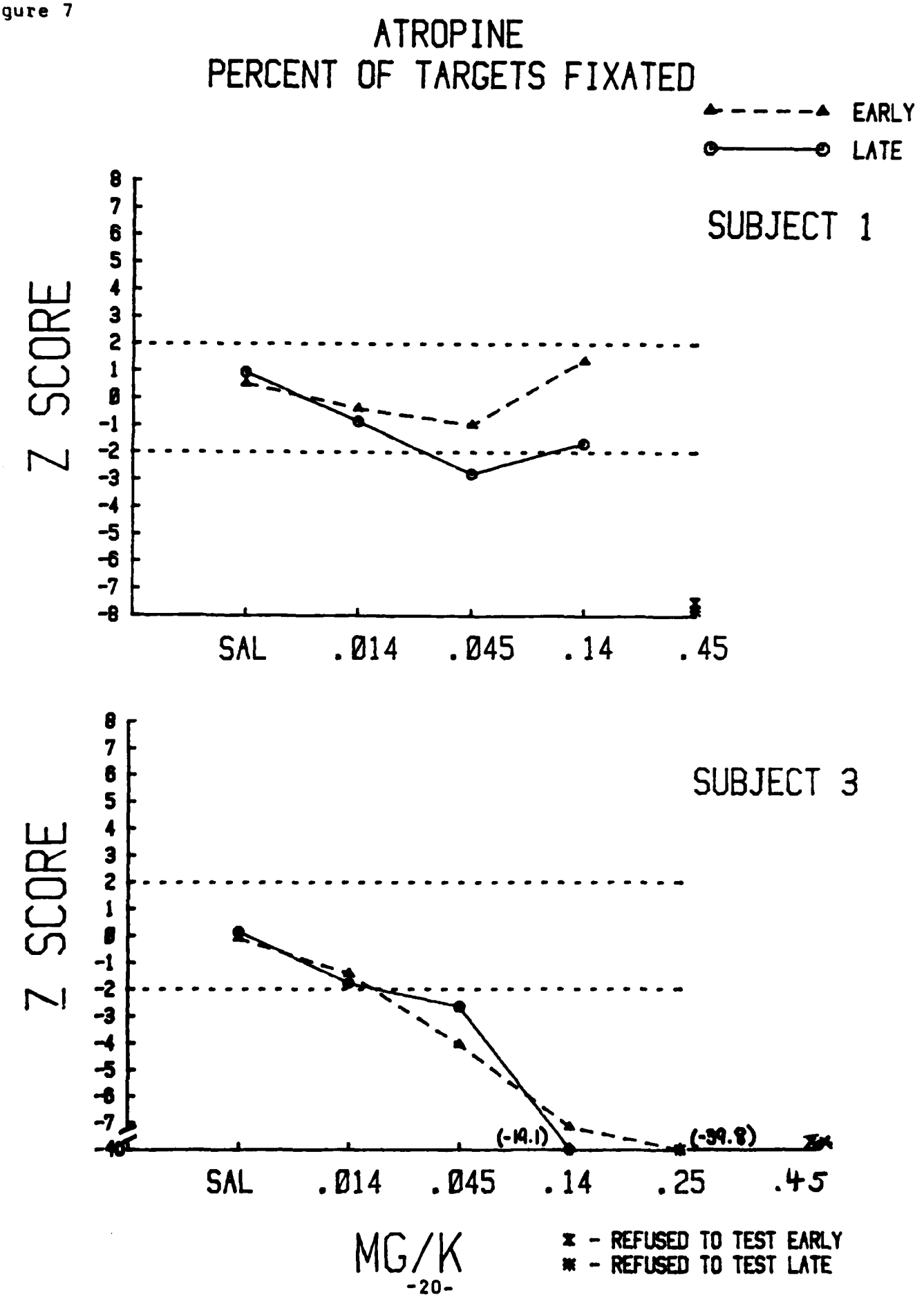
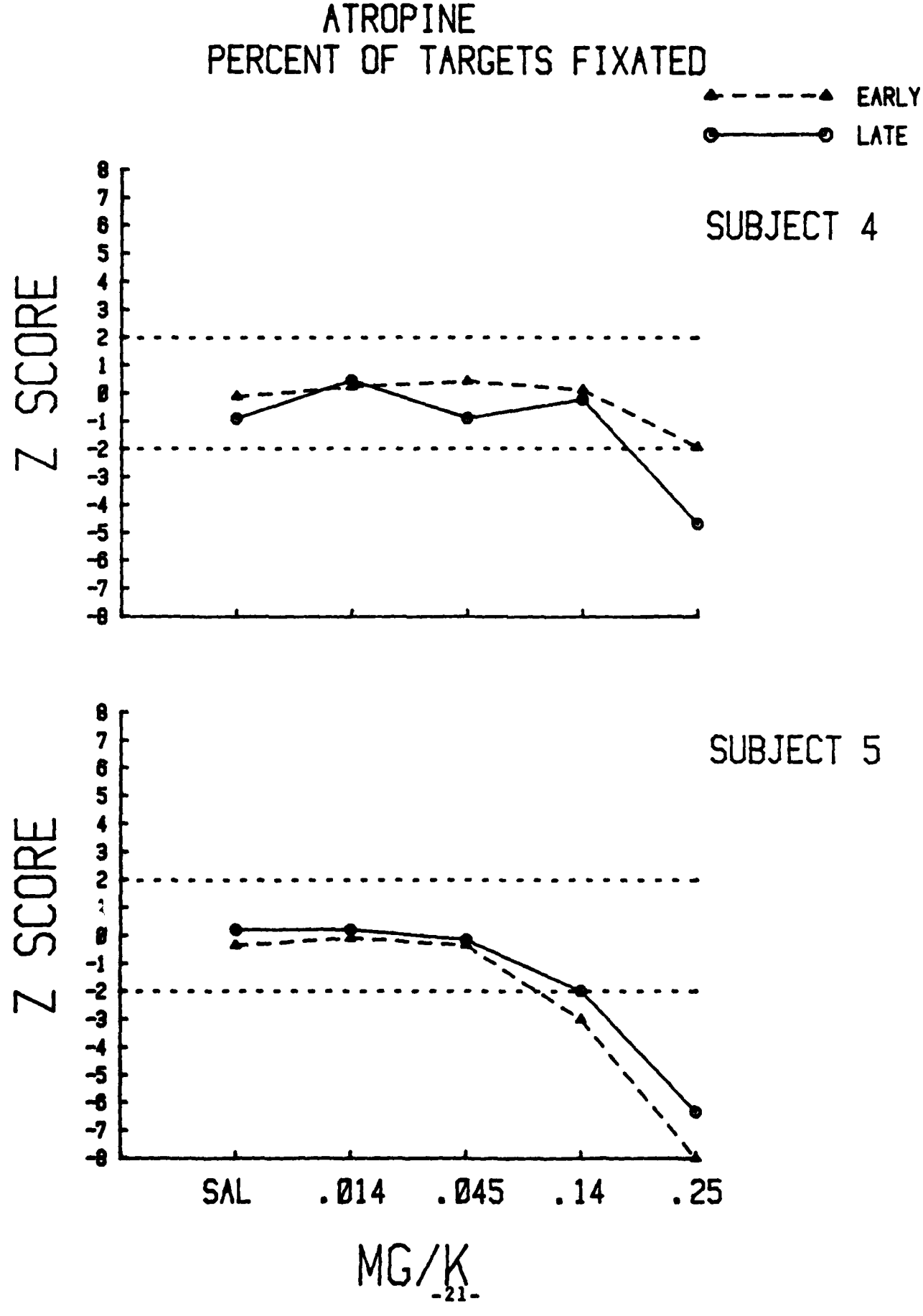
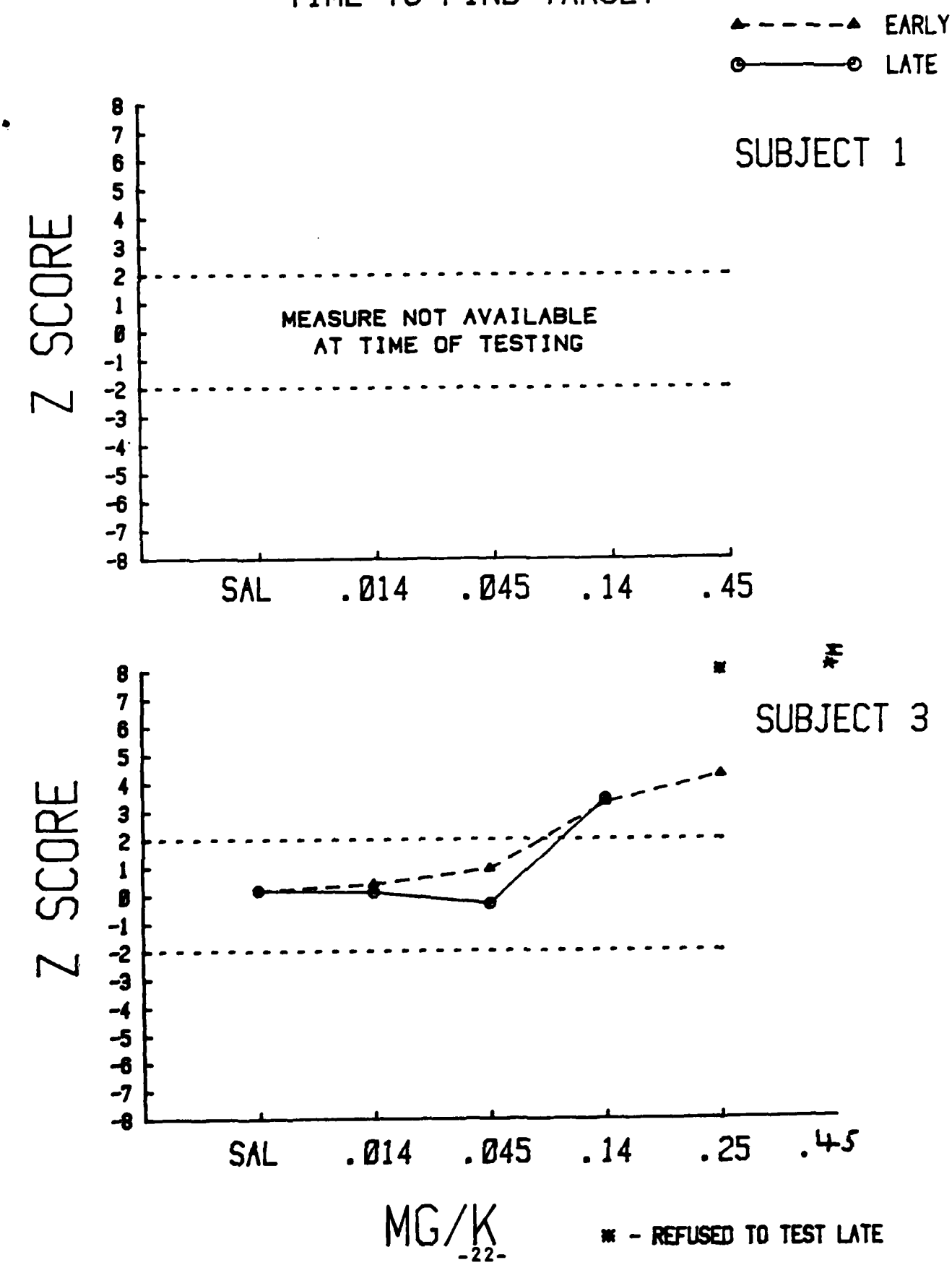


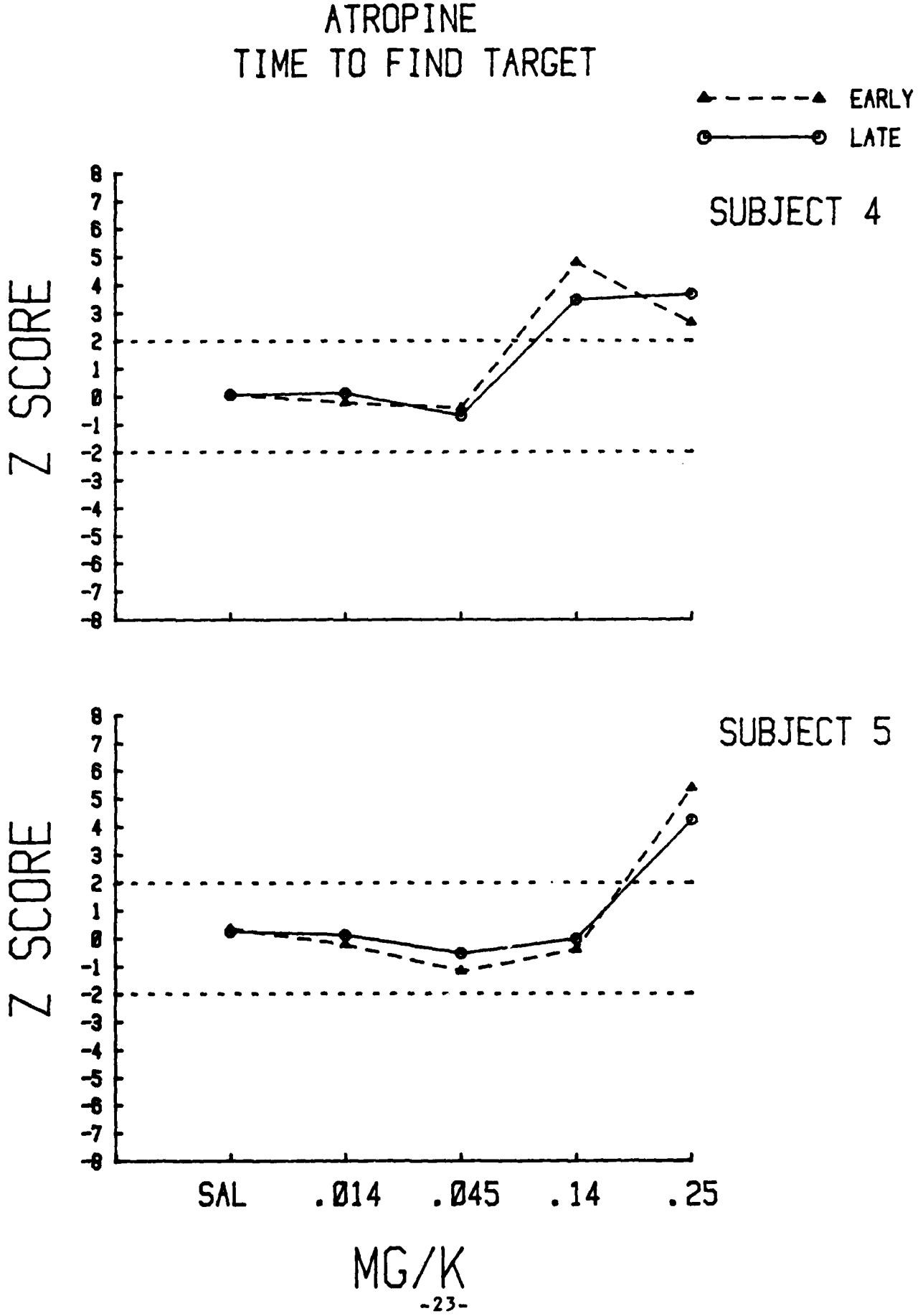
Figure 7


ATROPINE
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 1
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.45
SUBJECT 3
Z SCORE
(-14.1)
(-39.8)
SAL
.014
.045
.14
.25
.45
MG/K
x - REFUSED TO TEST EARLY
* - REFUSED TO TEST LATE

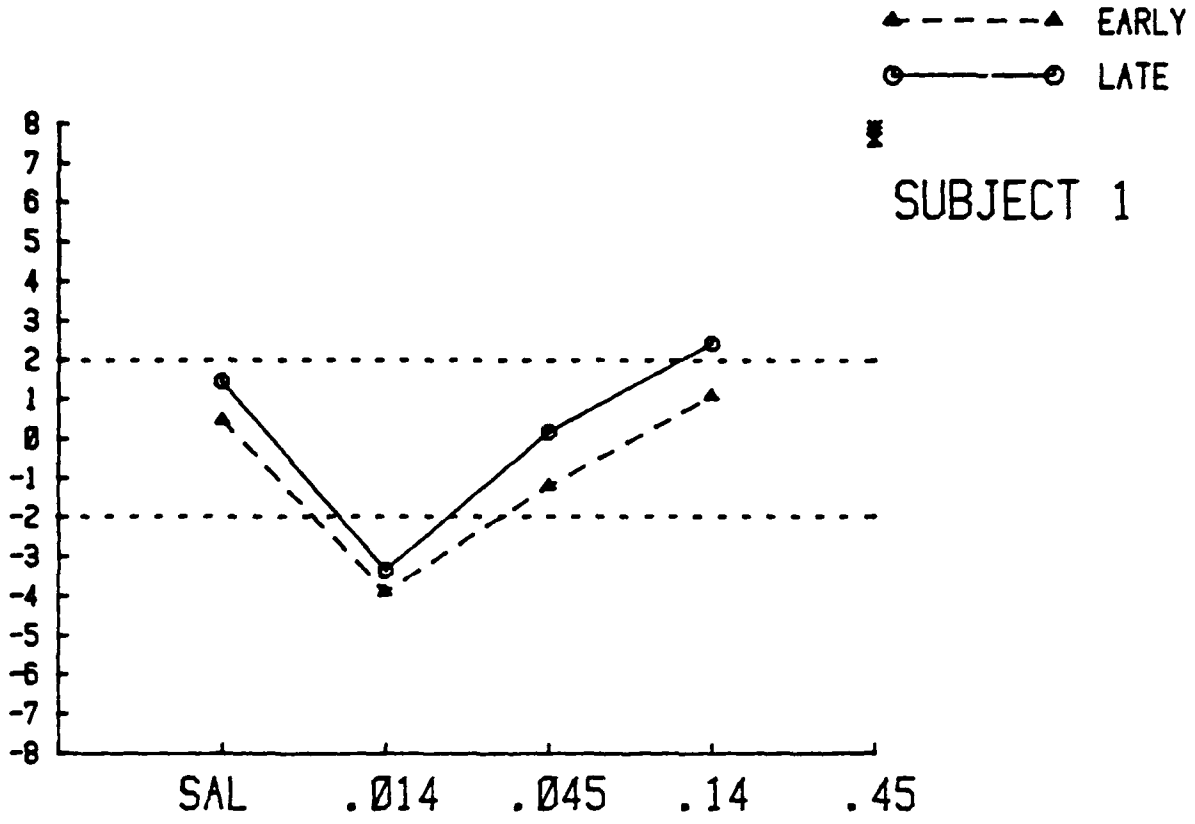

ATROPINE
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 4
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SUBJECT 5
Z SCORE
SAL
.014
.045
.14
.25
MG/K

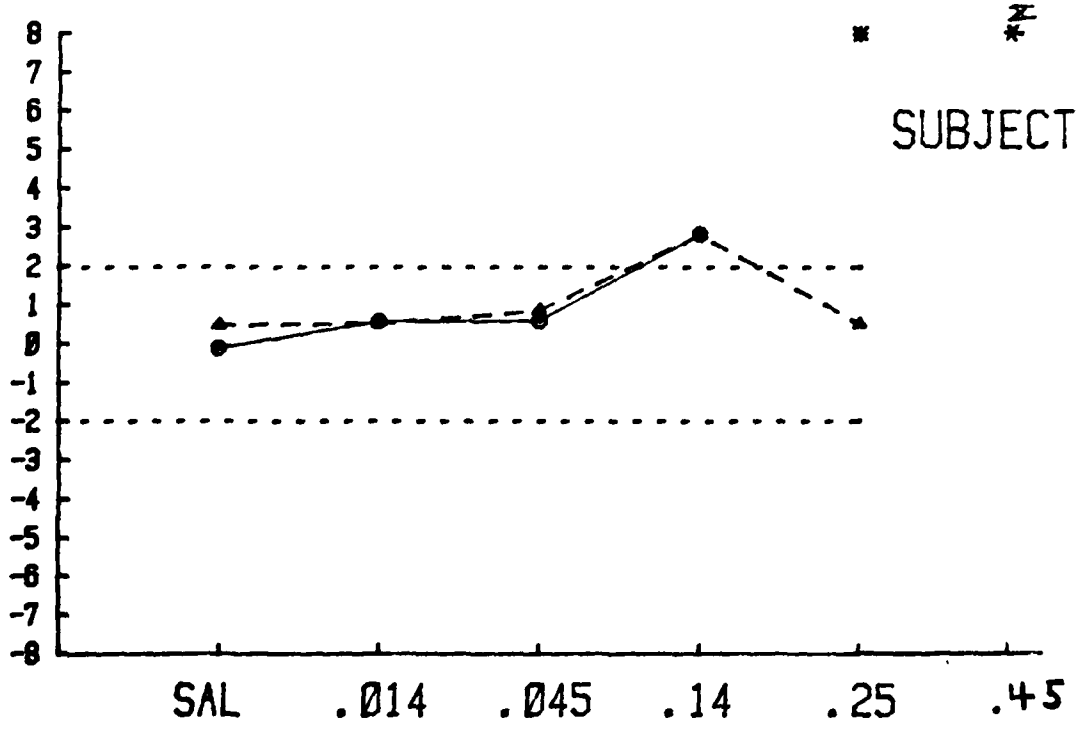
ATROPINE
TIME TO FIND TARGET




ATROPINE
TIME TO FIND TARGET
EARLY
LATE
SUBJECT 4
SUBJECT 5
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.014
.045
.14
.25
MG/K

ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET





MG/K

x - REFUSED TO TEST EARLY
* - REFUSED TO TEST LATE

ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

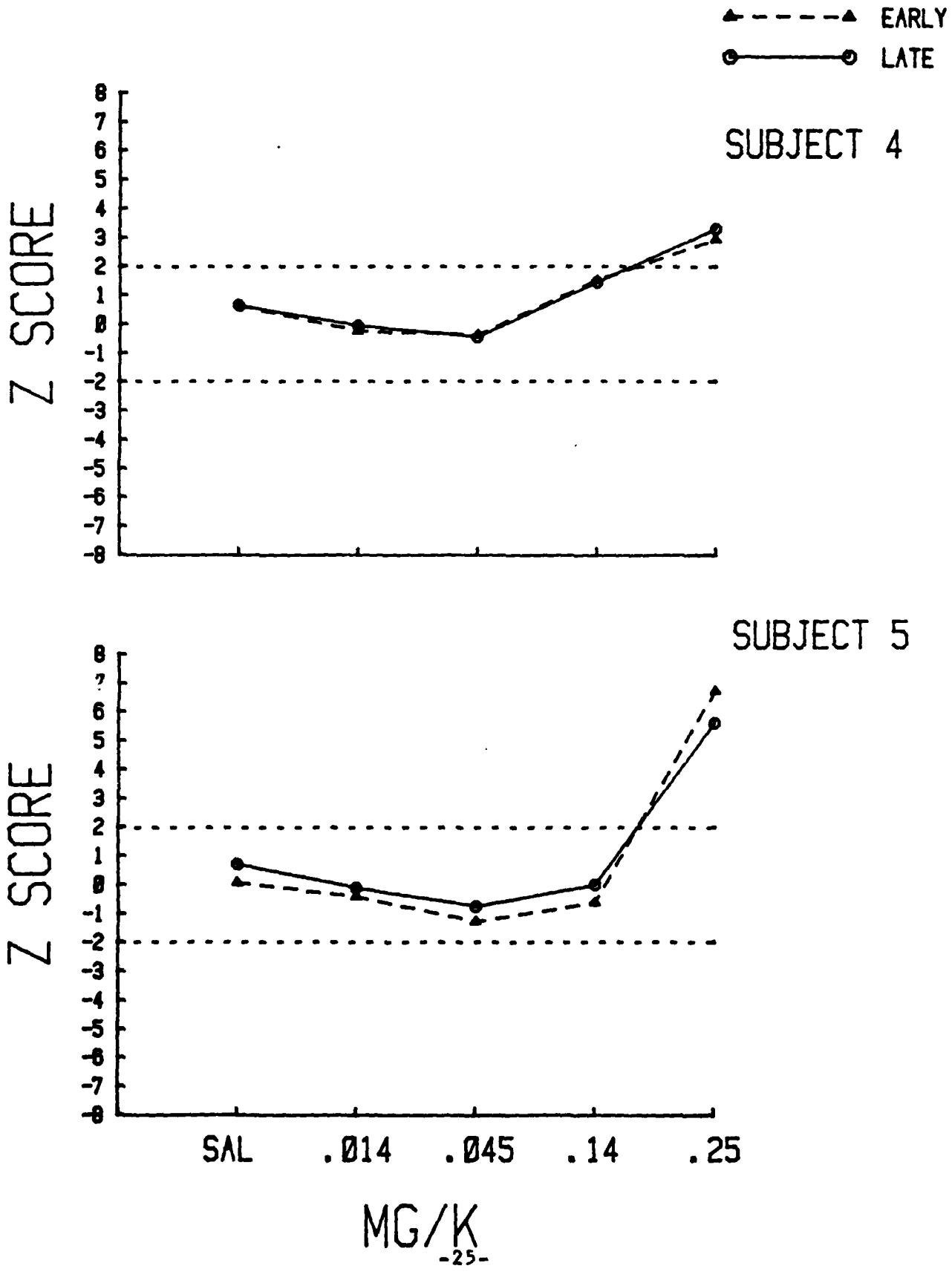


Table 4. Atropine

"Worst Case" Absolute Scores
Subject 3
Dose: .25 mg/K

	Baseline	Drug/Early	Drug/Late
Percent of targets fixated	98 ±2.1	14	*
ON SUCCESSFUL TRIALS:			
Reaction time to begin search (msec):	224 ±15	281	*
Time required to fixate target (msec)	444 ±37	603	*
Number of fixations required to fixate target	1.75 ±.14	1.8	*
Length of scan path to fixate target (radian distance in degrees of visual angle)	23.4 ±3	25.7	*

*Failed to test

BENACTYZINE

Table 5. Schedule of Completed Drug Trials

Dose A = .057 mg/K; B = .182; C = .57; D = Saline; E = 1.8

Subject 1	B	D	C	B	A	D	A	C	E	E	C		
	x	x	x	x	x	x	x	#	c	c	c		
Subject 2	A	D	A	B	C	B	C	D	E	E			
	#	x	x	x	x	x	x	x	x	x			
Subject 3	A	B	B	C	D	A	C	C	D	E	E	E	B
	x	x	x	c	c	c	c	c	c	#	c	c	c
Subject 4	D	D	A	B	A	B	C	C	E	E			
	c	c	c	c	c	c	c	c	c	c			
Subject 5	A	D	A	B	C	B	C	D	E	E	C		
	c	c	c	c	c	c	#	c	c	c	c		

Legend as in Table 3

.057 mg/K

Neurological Symptoms: Normal

Oculomotor Competence: Normal, except for tendency of subject 4 to close its eyes between trials. This produced a pattern of meandering eye movements that is normal for primates with eyes closed or otherwise in the dark.

Visual Search: Performance as a group was normal. One monkey had interludes of not testing. This subject (our most erratic monkey) alone suffered a notable drop in the number of successful trials, and a slight increase in the number of fixations required to find the target.

.182 mg/K

Neurological Symptoms: Normal, except for a suspicion of mydriasis in two subjects.

Oculomotor Competence: Normal, but for previously mentioned wandering movements between trials.

Visual Search: Performance as a group was normal, but there were individual differences. One subject (3) refused to test during the Early session of one of the two tests of this dosage. Early data could not be collected from a second (2) due to the chronic difficulty in calibrating this monkey. The other 3 subjects tested consistently. Two of these had a borderline decrement in rate of success and number of fixations to find the target during the Early session. Their performance improved abruptly at 37 minutes after injection.

.57 mg/K

Neurological Symptoms: Normal, but for slight mydriasis in one subject.

Oculomotor Competence: The Early session contained fractured fixations (duration: 477 vs. 735 ± 46), mildly abnormal drift in fixations (20 vs. 17 ± 1.6 min.) and longer saccades. The oculomotor record improved during the Late session.

Visual Search: Benactyzine's main effect was to bring testing to a halt. Three of the four monkeys refused to test at all during the Early session. The fourth made some effort to find the targets on trials triggered by us. Its resulting performance was deficient on all measures shown in the graphs.

All animals resumed testing during the Late session (>35 min.) and performed rather well. Two subjects had fewer successful trials but otherwise and as a group performance was normal.

1.82 mg/K

Neurological Symptoms: Mild mydriasis appeared in two subjects but there were no other symptoms.

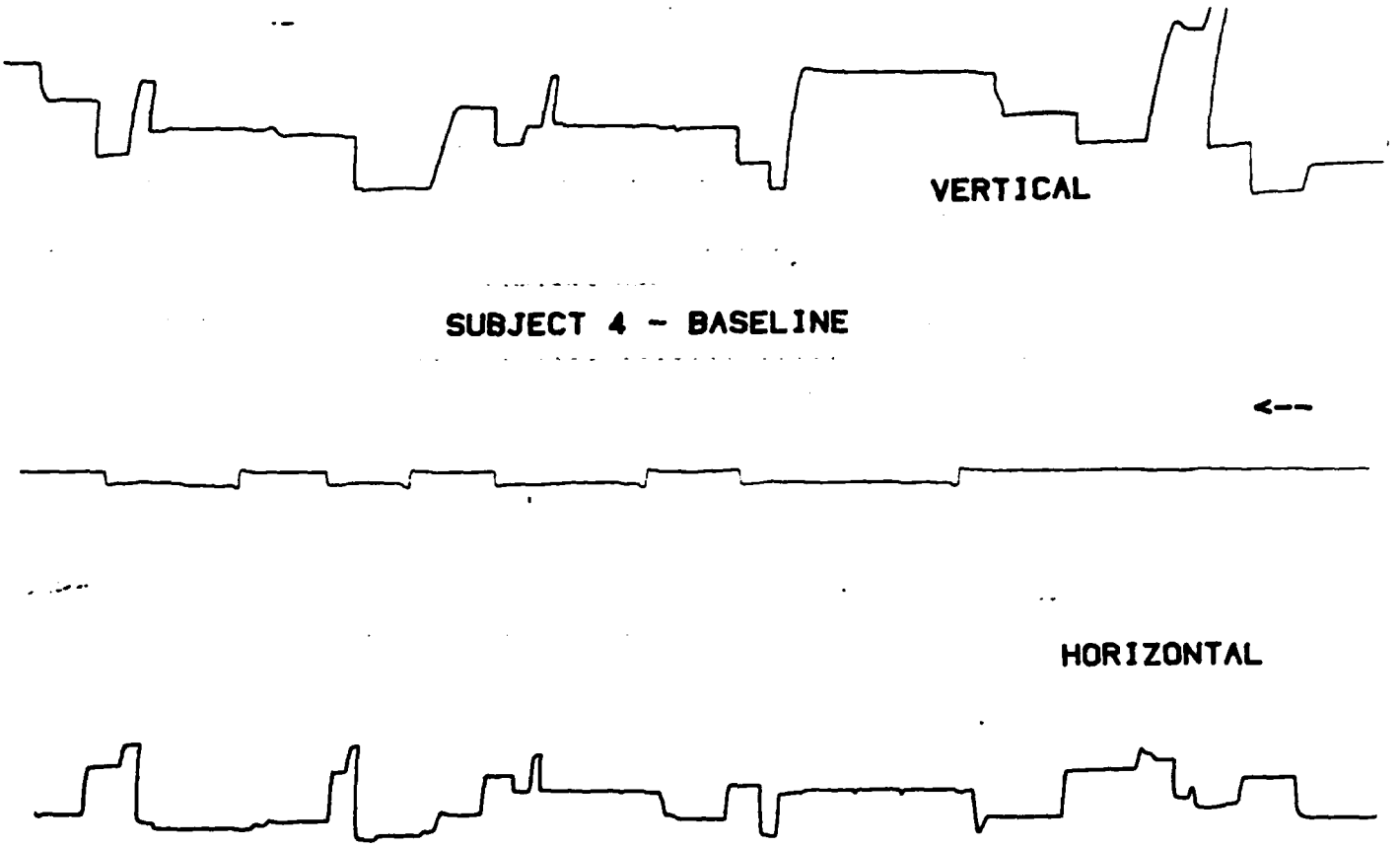
Oculomotor Competence: The record was similar to that at .57 mg/K. The Early session was marked by slow wandering movements and short drifting fixations. The record improved visibly during the Late session but analysis indicated mildly excessive drift in fixations and prolonged saccades.

Visual Search: All monkeys failed to test during the Early session and remained inattentive to trials triggered by us. Most resumed pressing the lever at 45-50 minutes after injection.

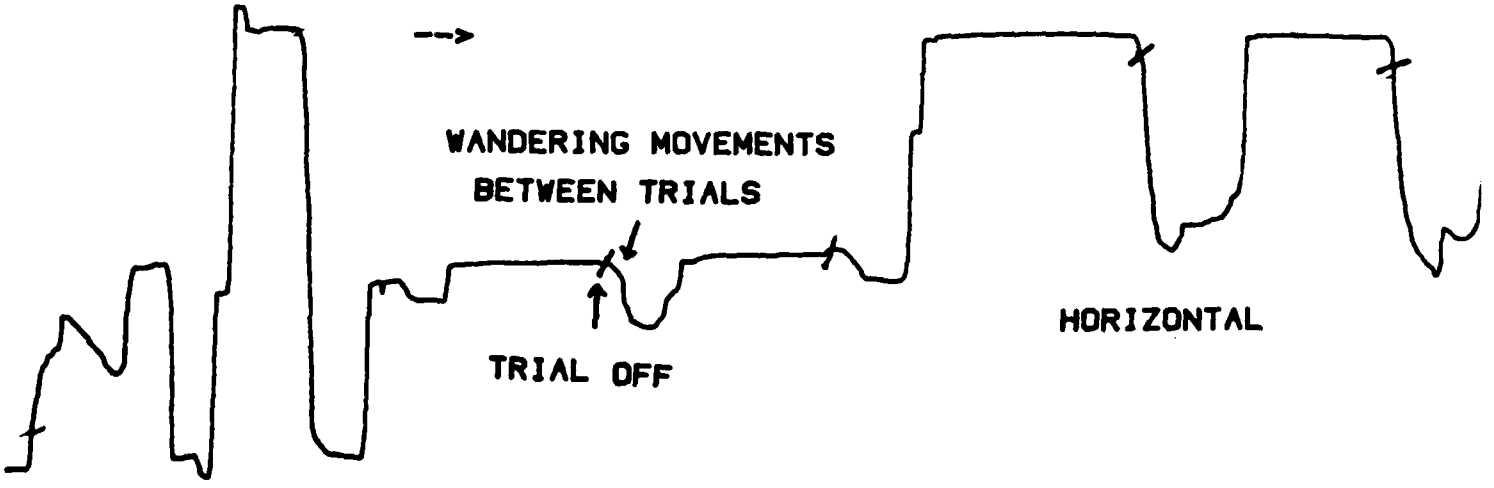
Once testing resumed, as a group the animals carried out visual search fairly well. The worst case was subject 4, who nonetheless found the target on 80% of the trials and needed only an extra 167 milliseconds to foveate it. Another subject (2) had a slight decrement and two of the monkeys performed within normal limits.

In summary, benactyzine at the highest doses is free of gross neurological effects. Its oculomotor sequelae are truncated,drifting fixations and prolonged saccades. These are most pronounced in the first half hour. The effect of the drug on Visual Search is to halt testing for 35-40 minutes and thereafter to leave performance relatively unscathed.

Figure 8 OCULOMOTOR RECORD - BENACTYZINE



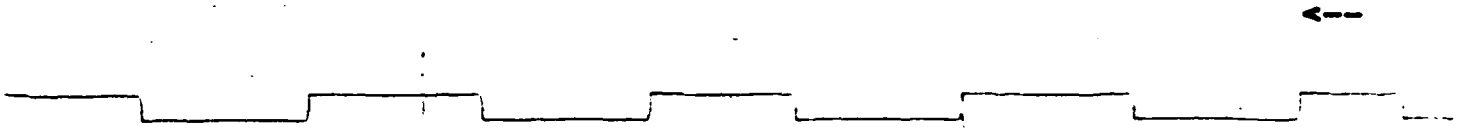
SUBJECT 4 - BENACTYZINE - .057 MG/K



SUBJECT 4 - BENACTYZINE - .57 MG/K - EARLY

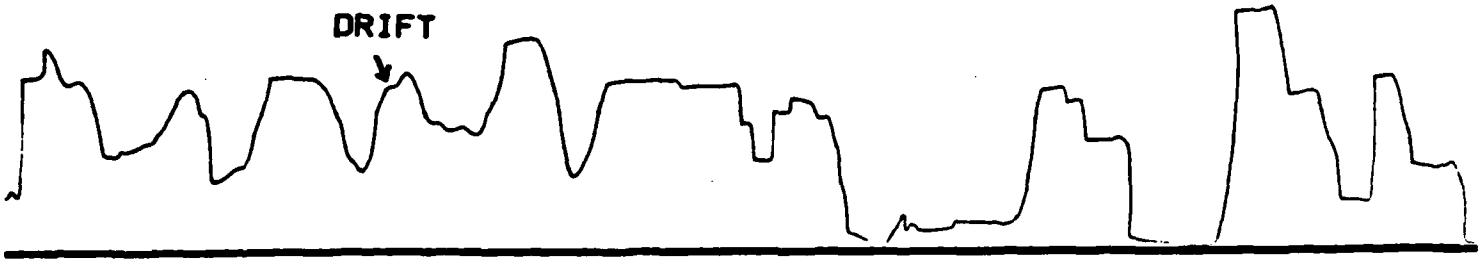
VERTICAL

WANDERING MOVEMENTS BETWEEN TRIALS

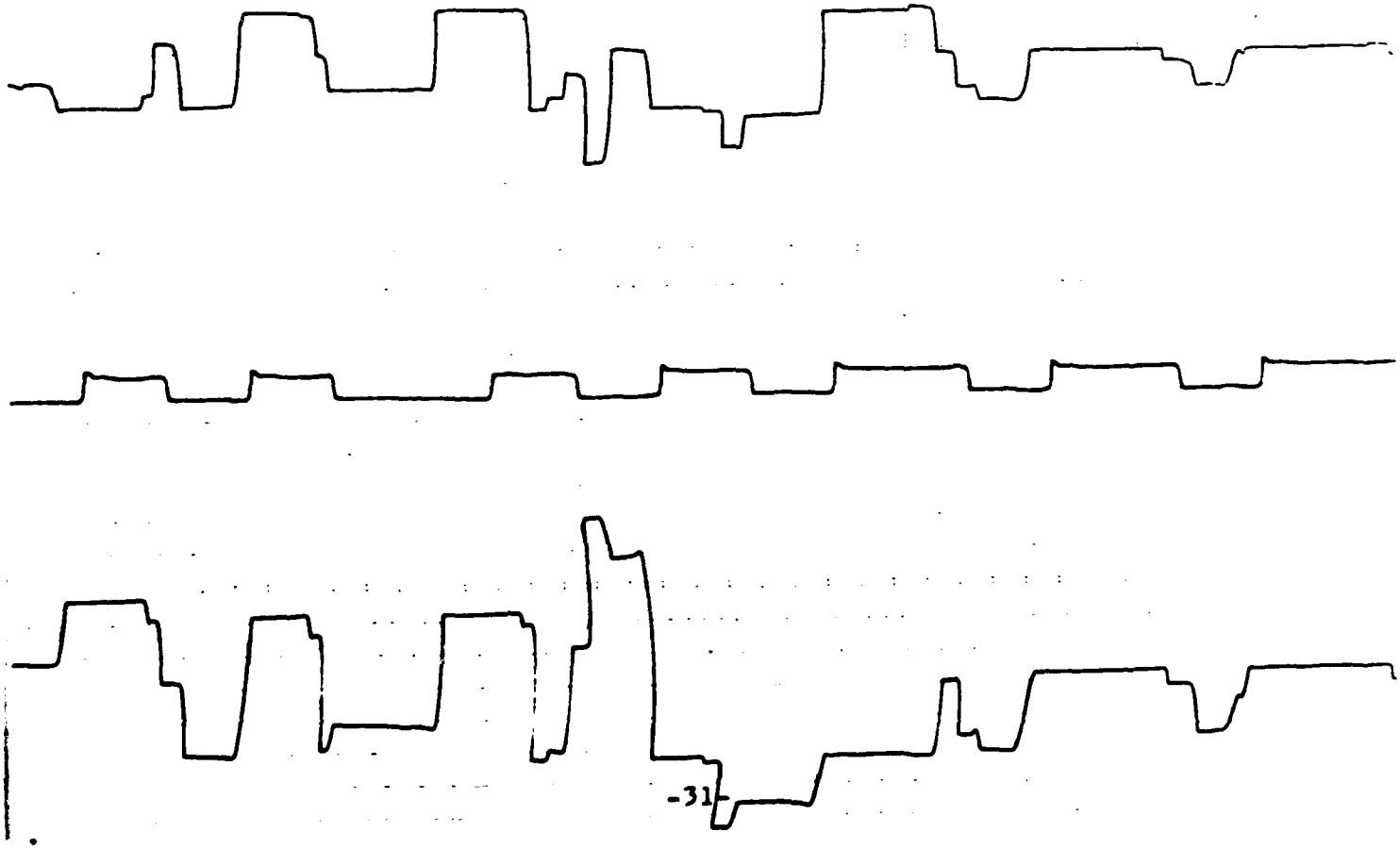


HORIZONTAL

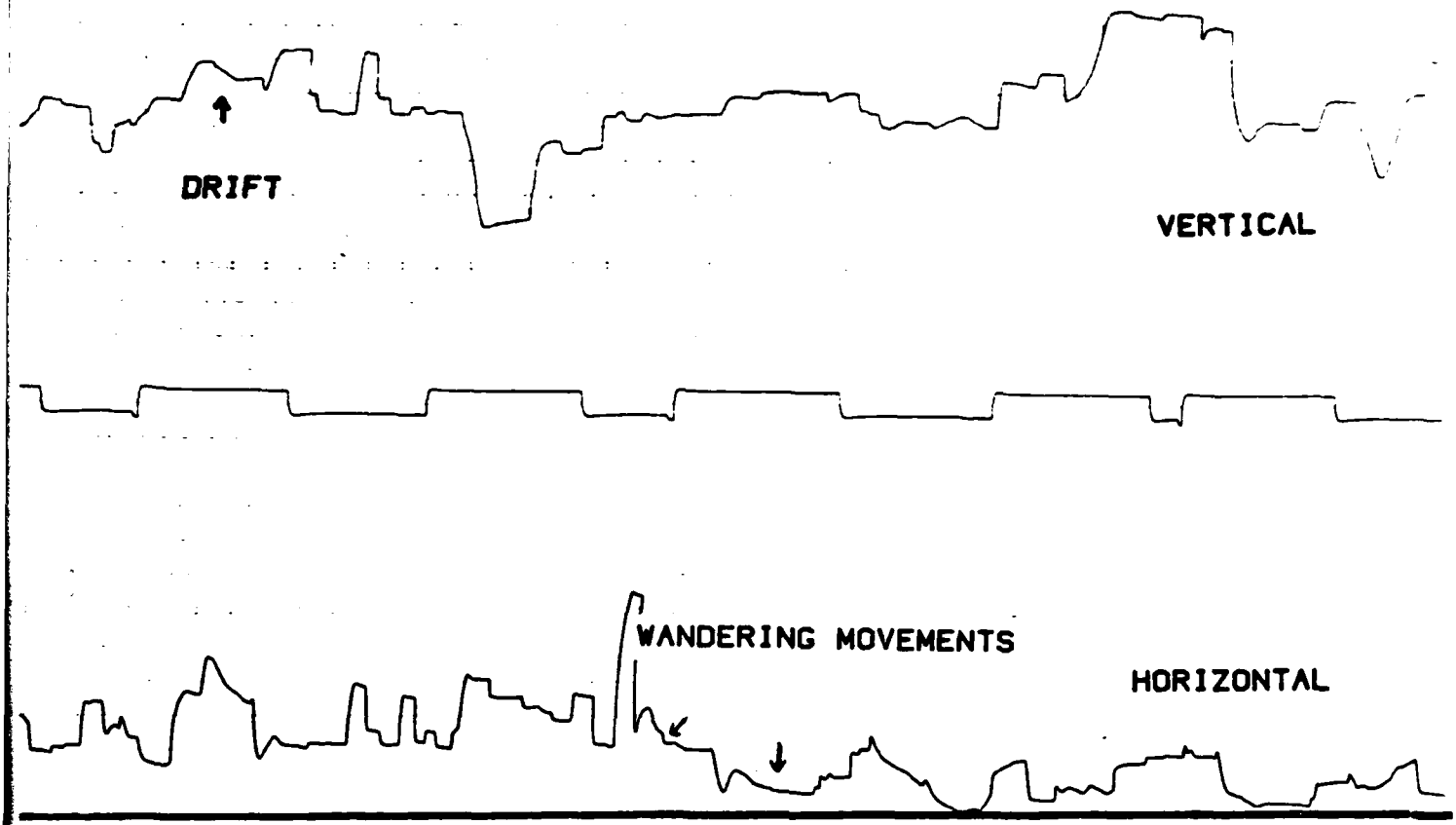
DRIFT



SUBJECT 4 - BENACTYZINE - .57 MG/K - LATE



SUBJECT 4 - BENACTYZINE - 1.8 MG/K - EARLY



SUBJECT 4 - BENACTYZINE - 1.8 MG/K - LATE

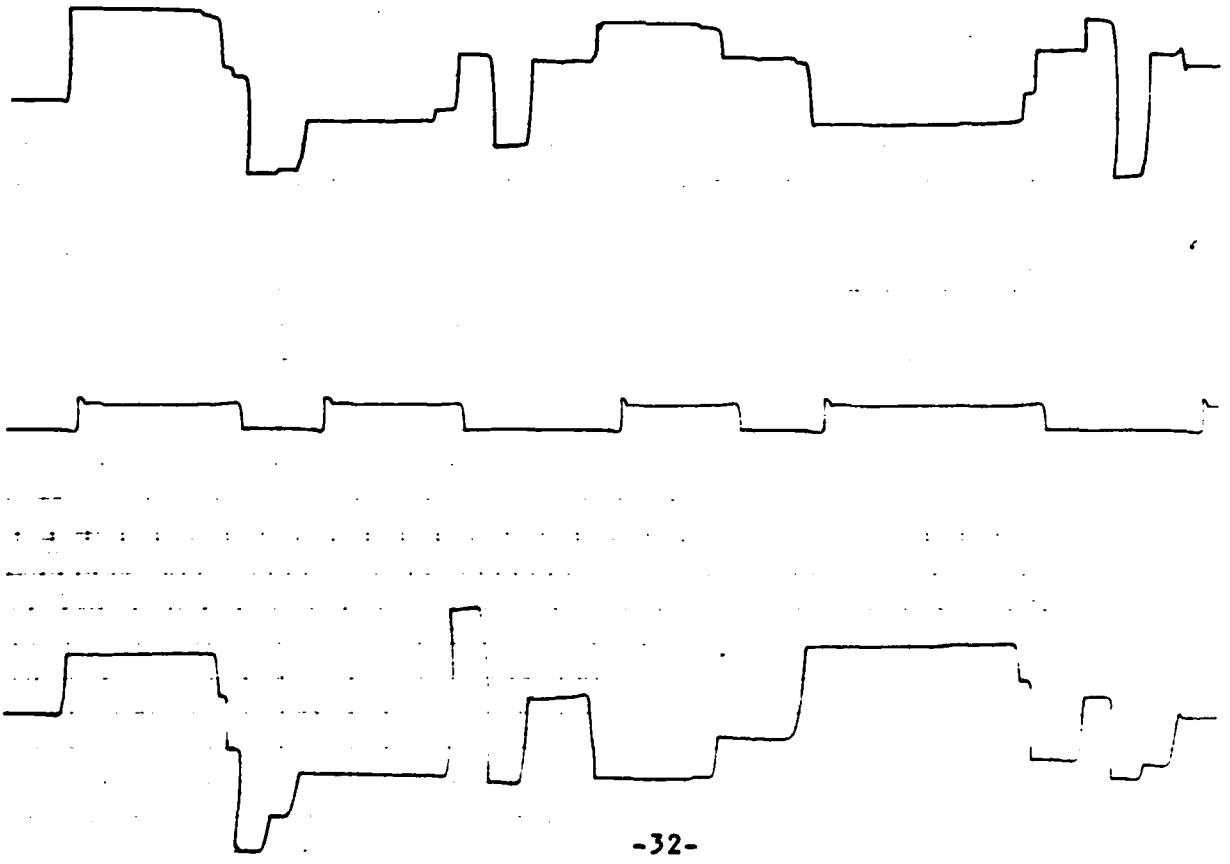
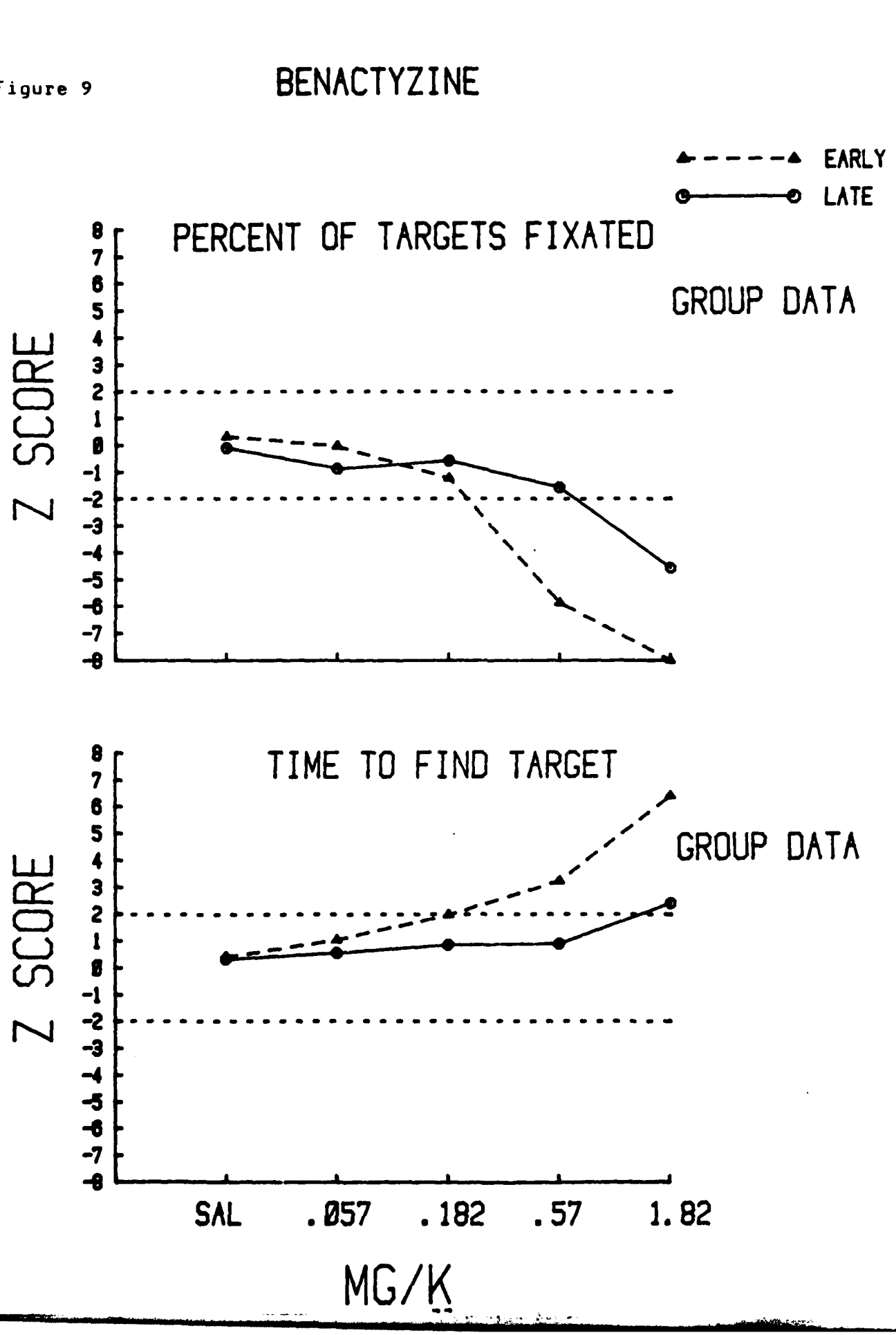


Figure 9


BENACTYZINE
EARLY
LATE
PERCENT OF TARGETS FIXATED
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
TIME TO FIND TARGET
GROUP DATA
Z SCORE
SAL
.057
.182
.57
1.82
MG/K

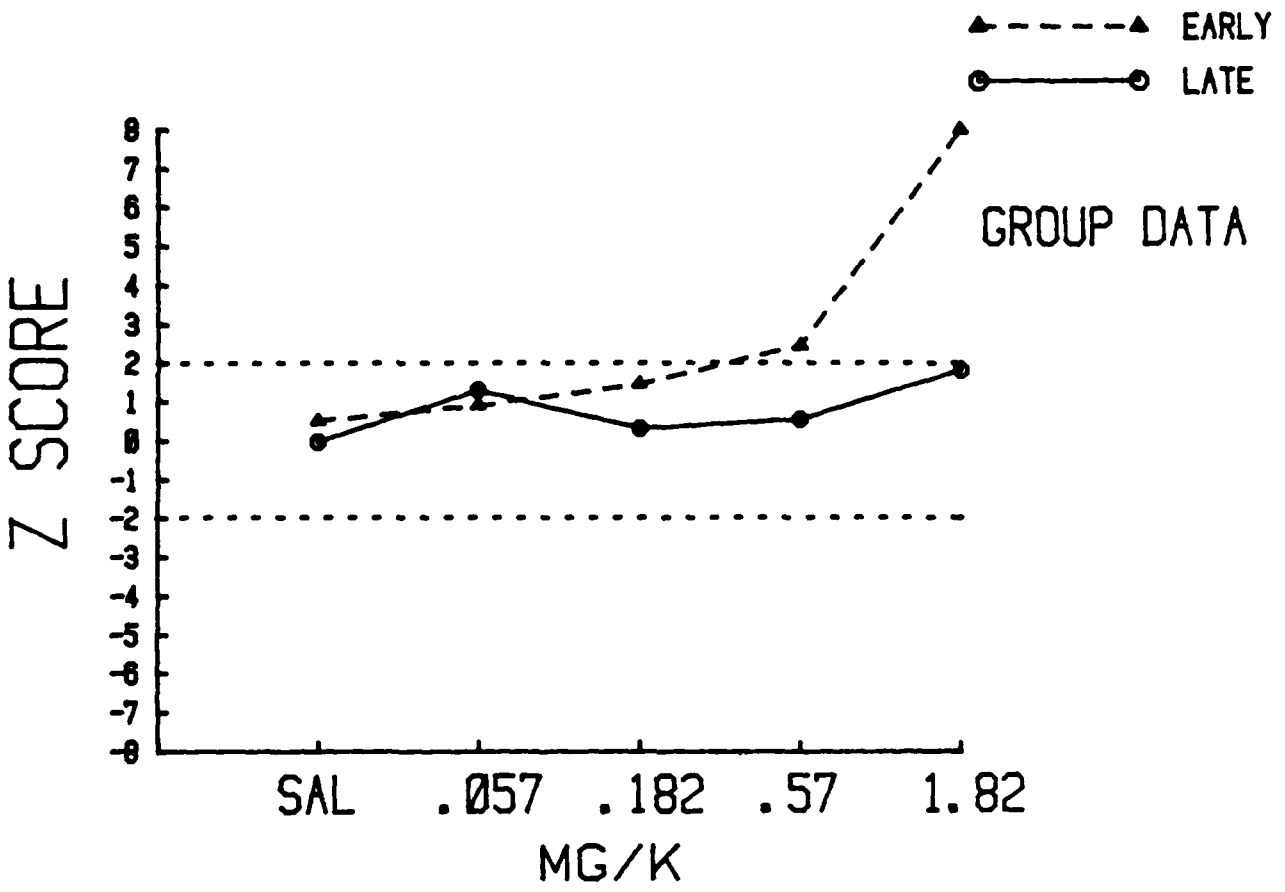
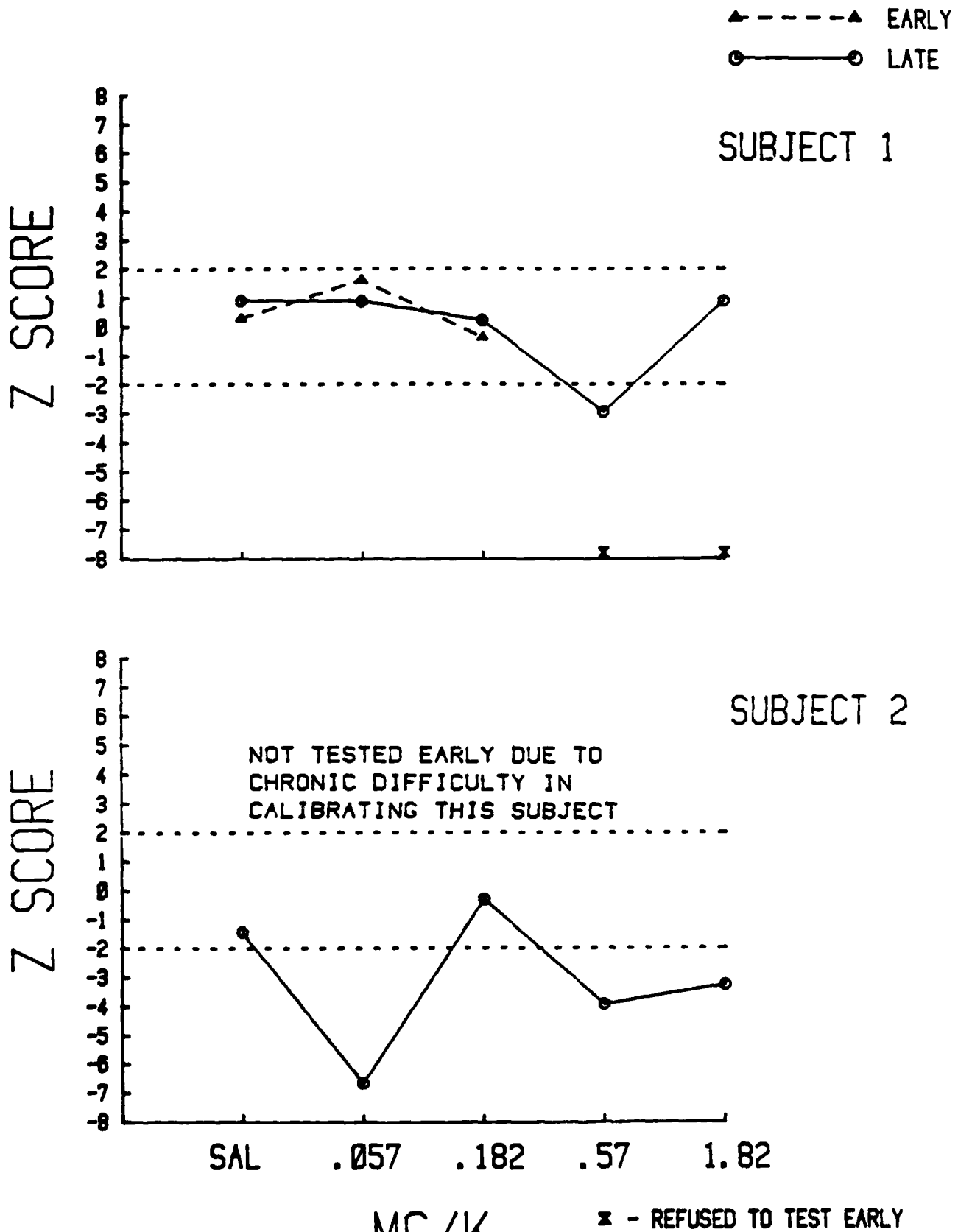
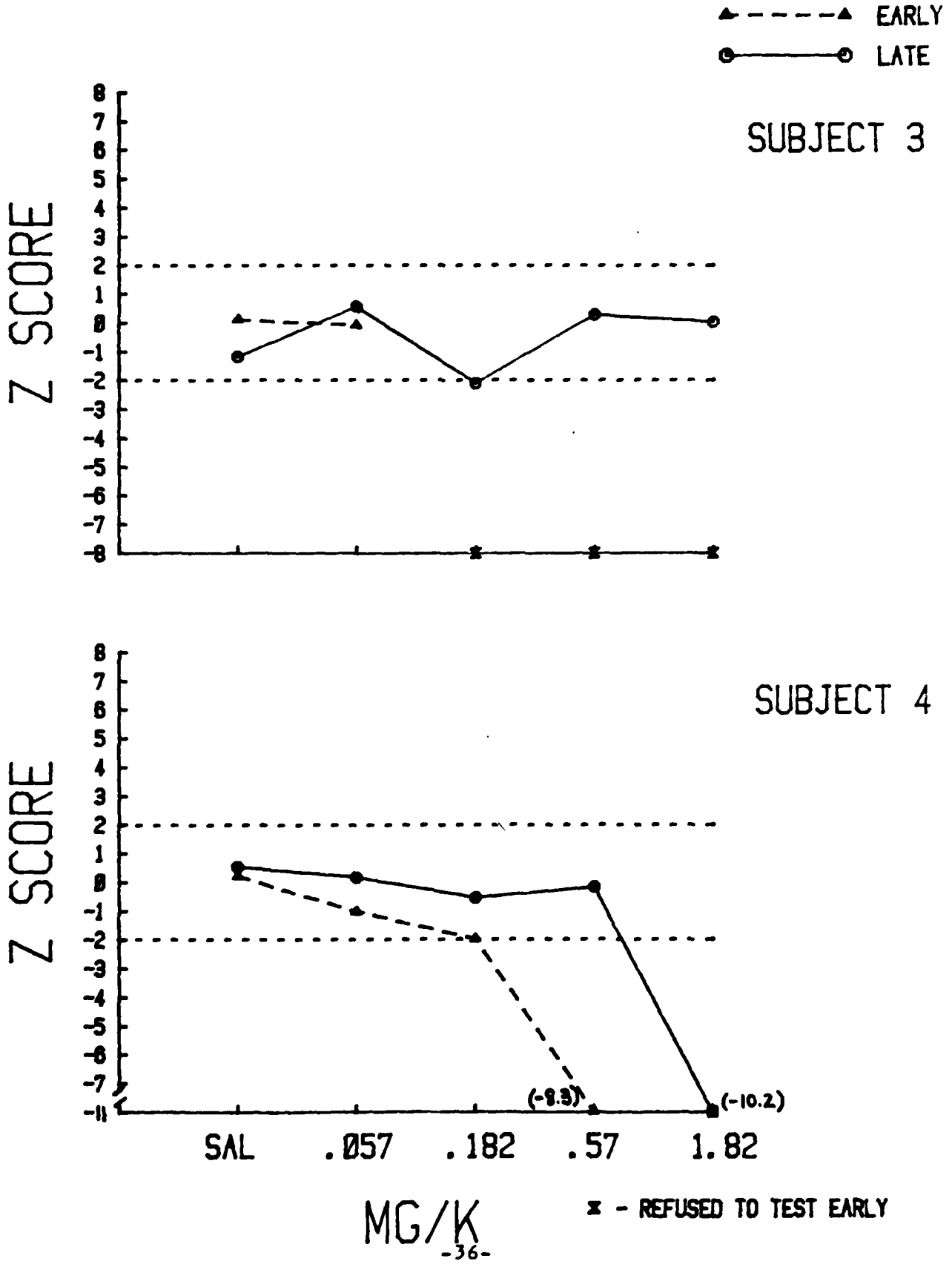

BENACTYZINE
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.057
.182
.57
1.82
MG/K

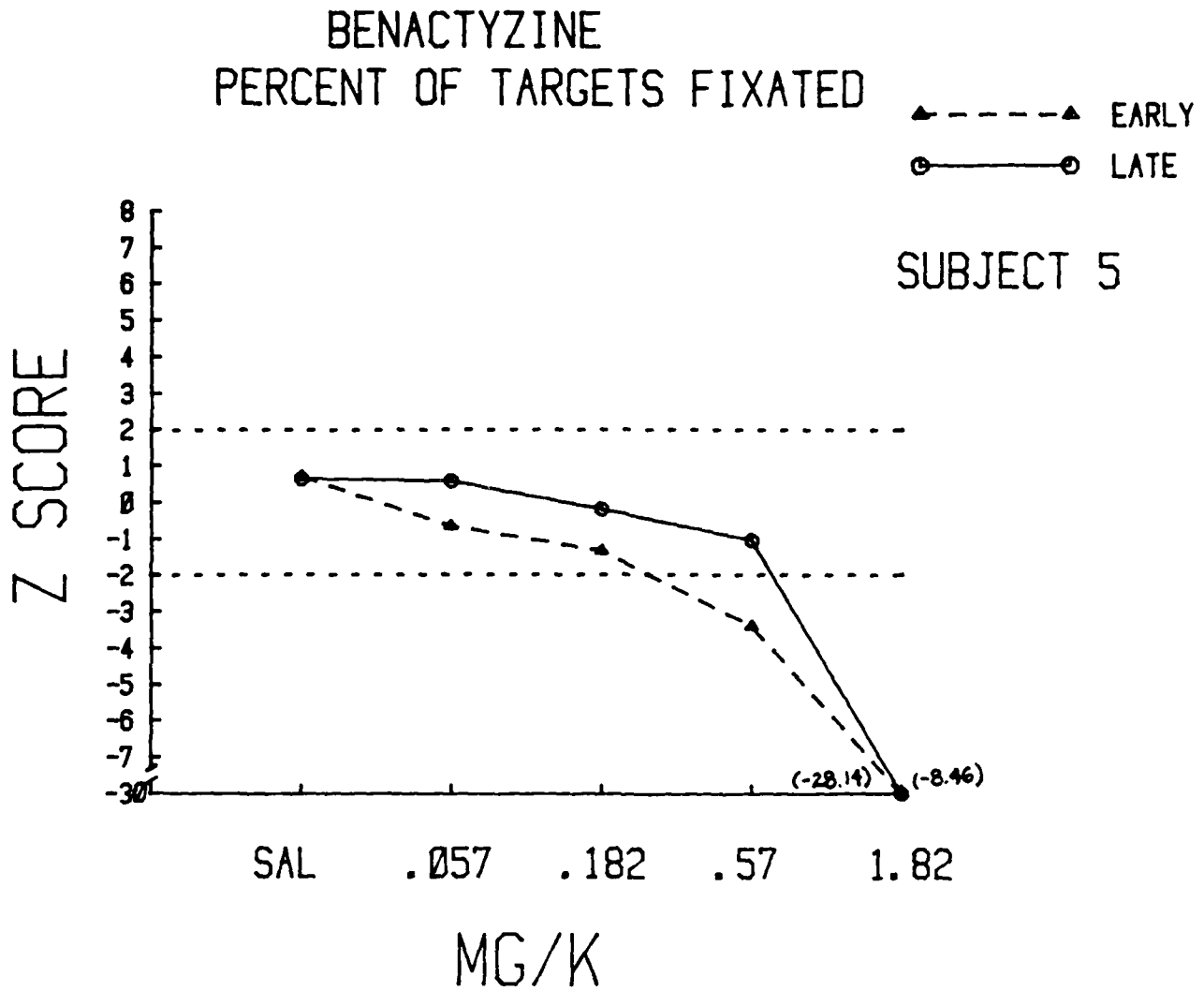
Figure 10

BENACTYZINE
PERCENT OF TARGETS FIXATED

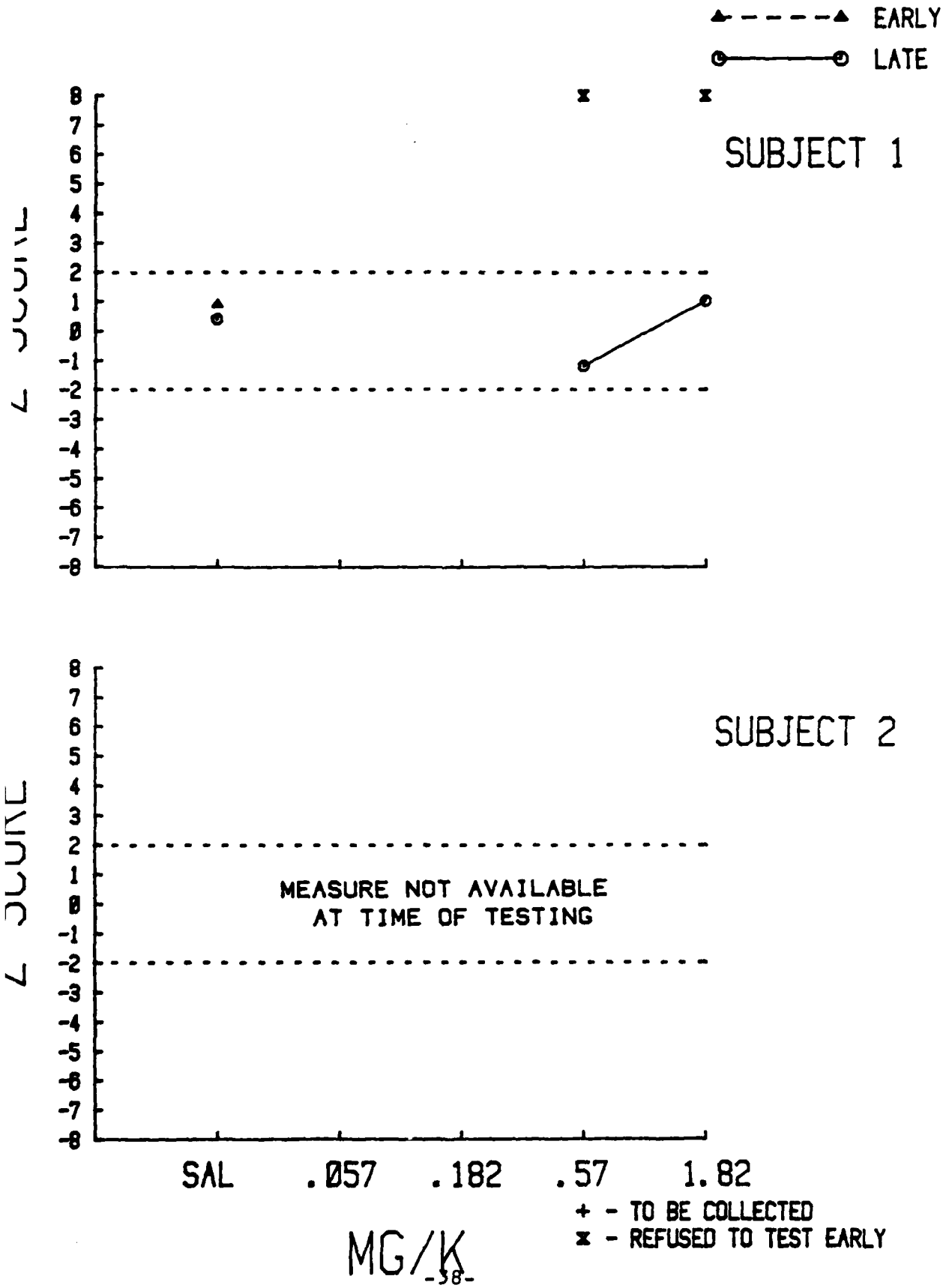


BENACTYZINE
PERCENT OF TARGETS FIXATED

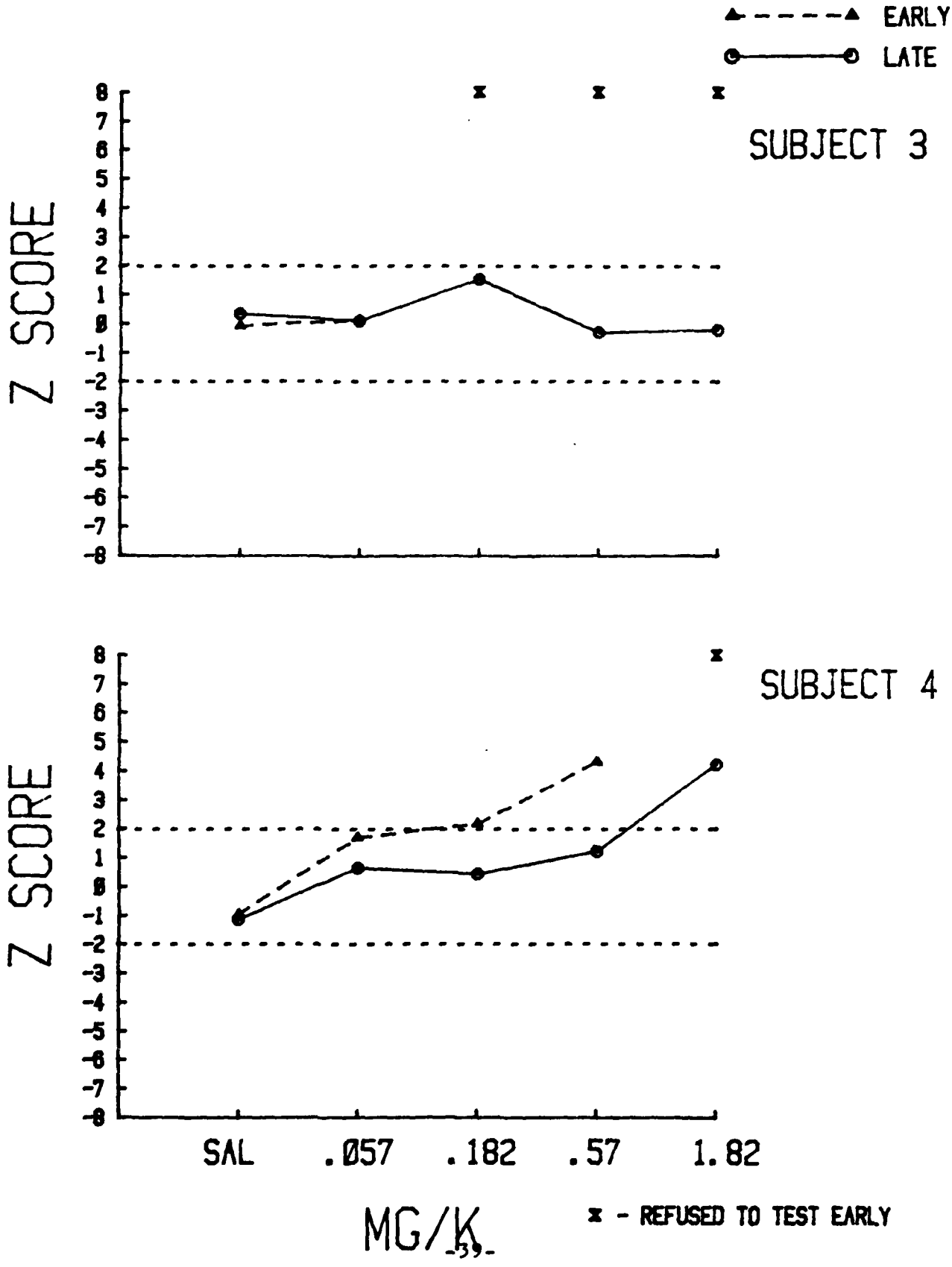


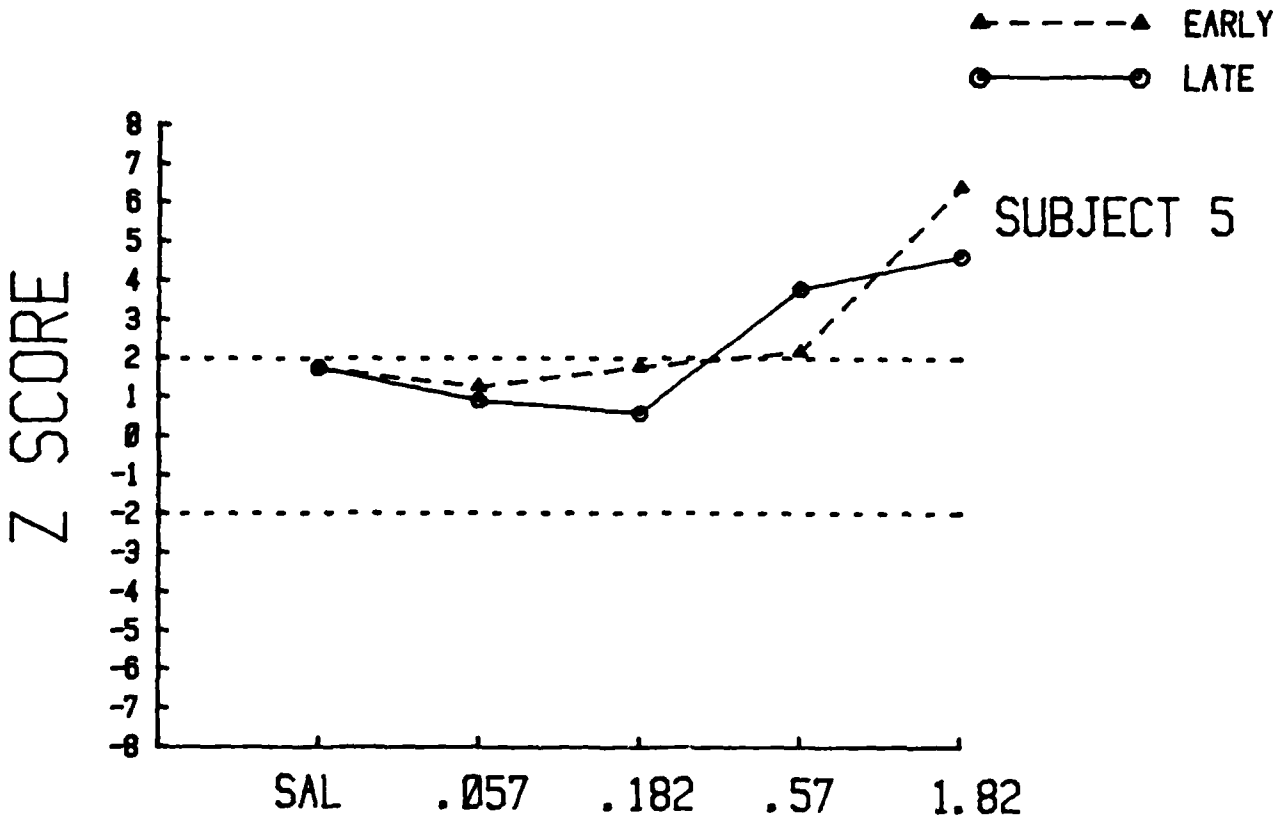

BENACTYZINE
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 5
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-30
(-28.14)
(-8.46)
SAL
.057
.182
.57
1.82
MG/K

BENACTYZINE
TIME TO FIND TARGET

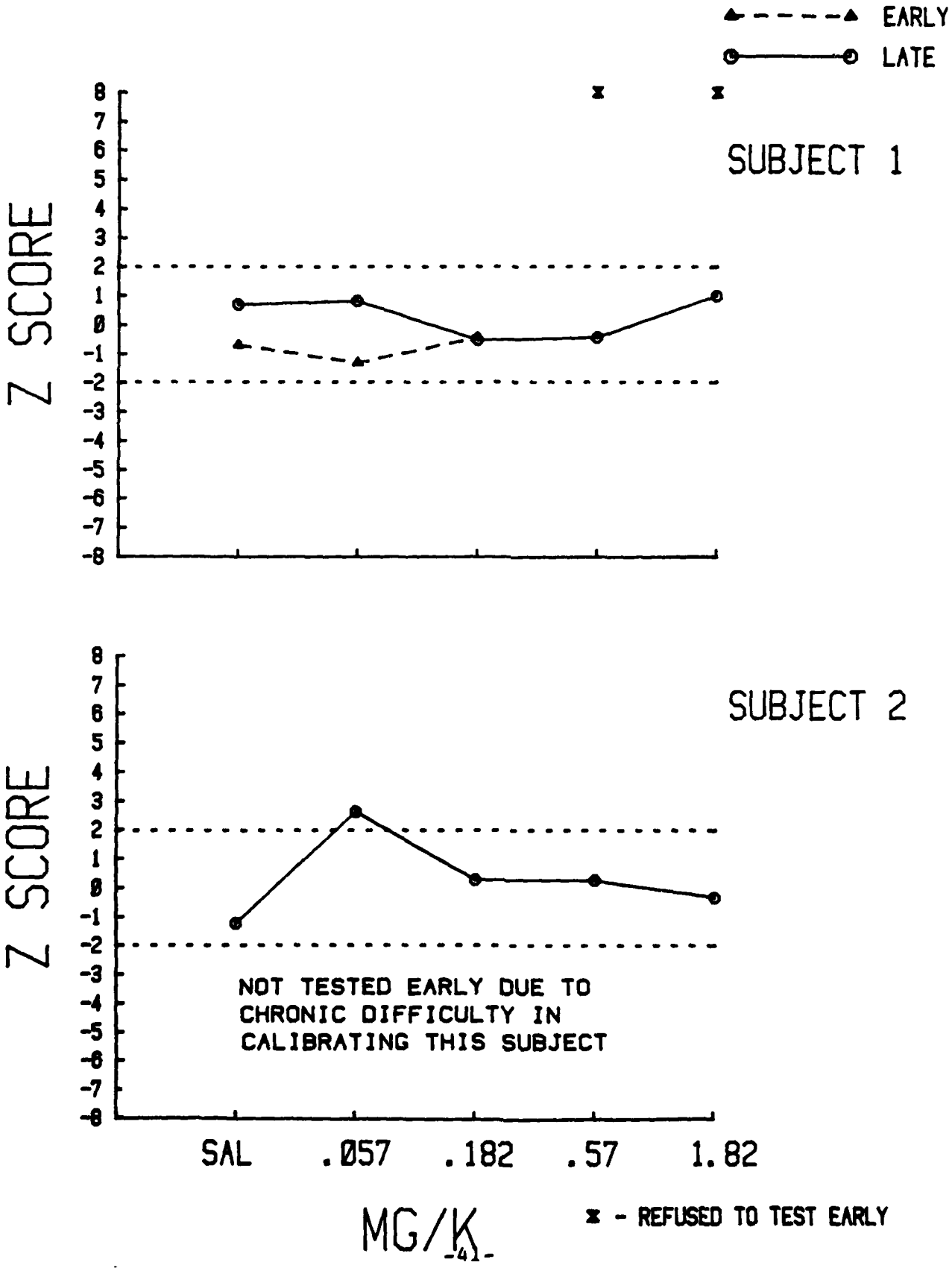


BENACTYZINE
TIME TO FIND TARGET

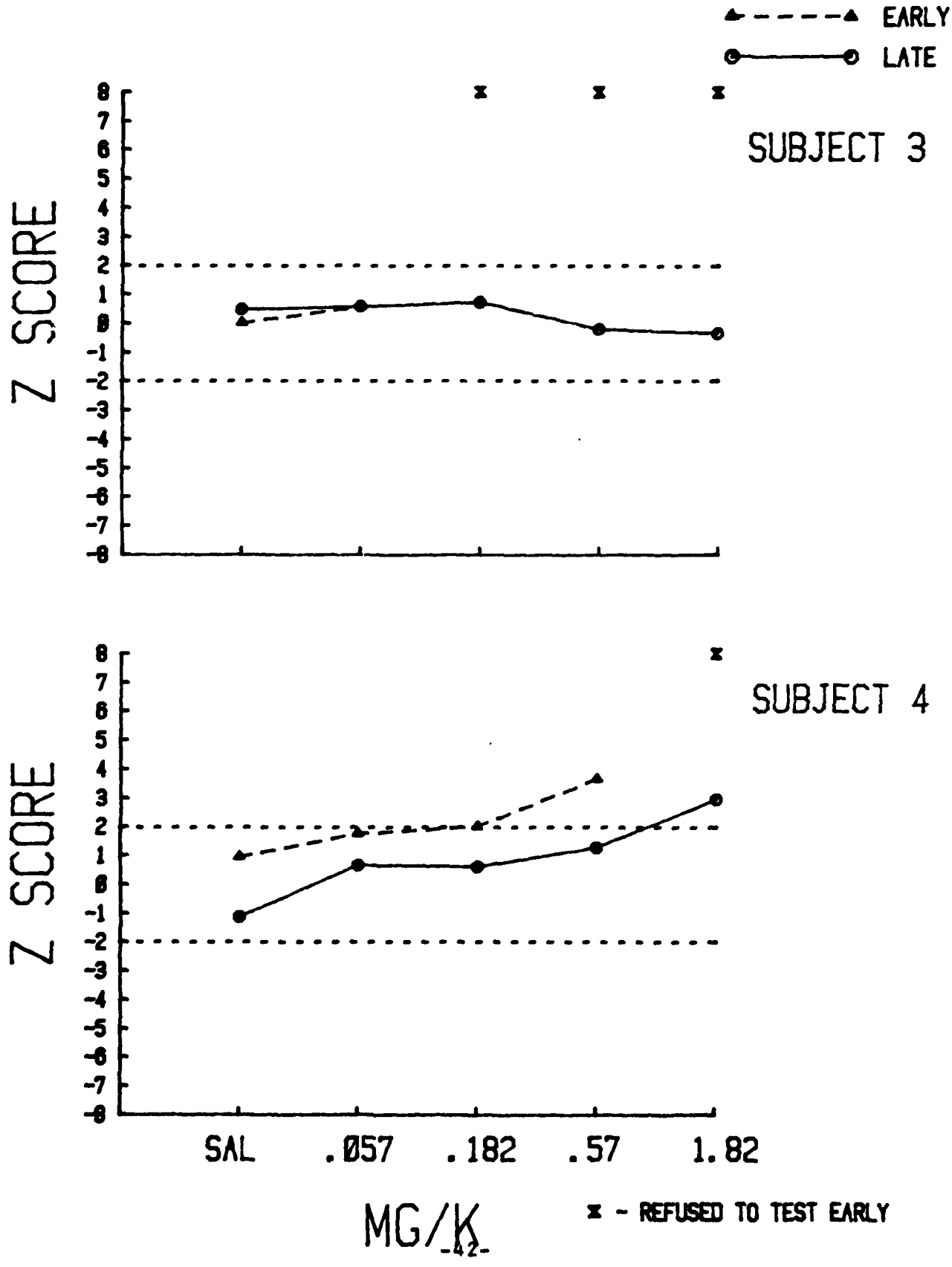



BENACTYZINE
TIME TO FIND TARGET
EARLY
LATE
SUBJECT 5
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.057
.182
.57
1.82

BENACTYZINE
NUMBER OF FIXATIONS TO FIND TARGET



BENACTYZINE
NUMBER OF FIXATIONS TO FIND TARGET



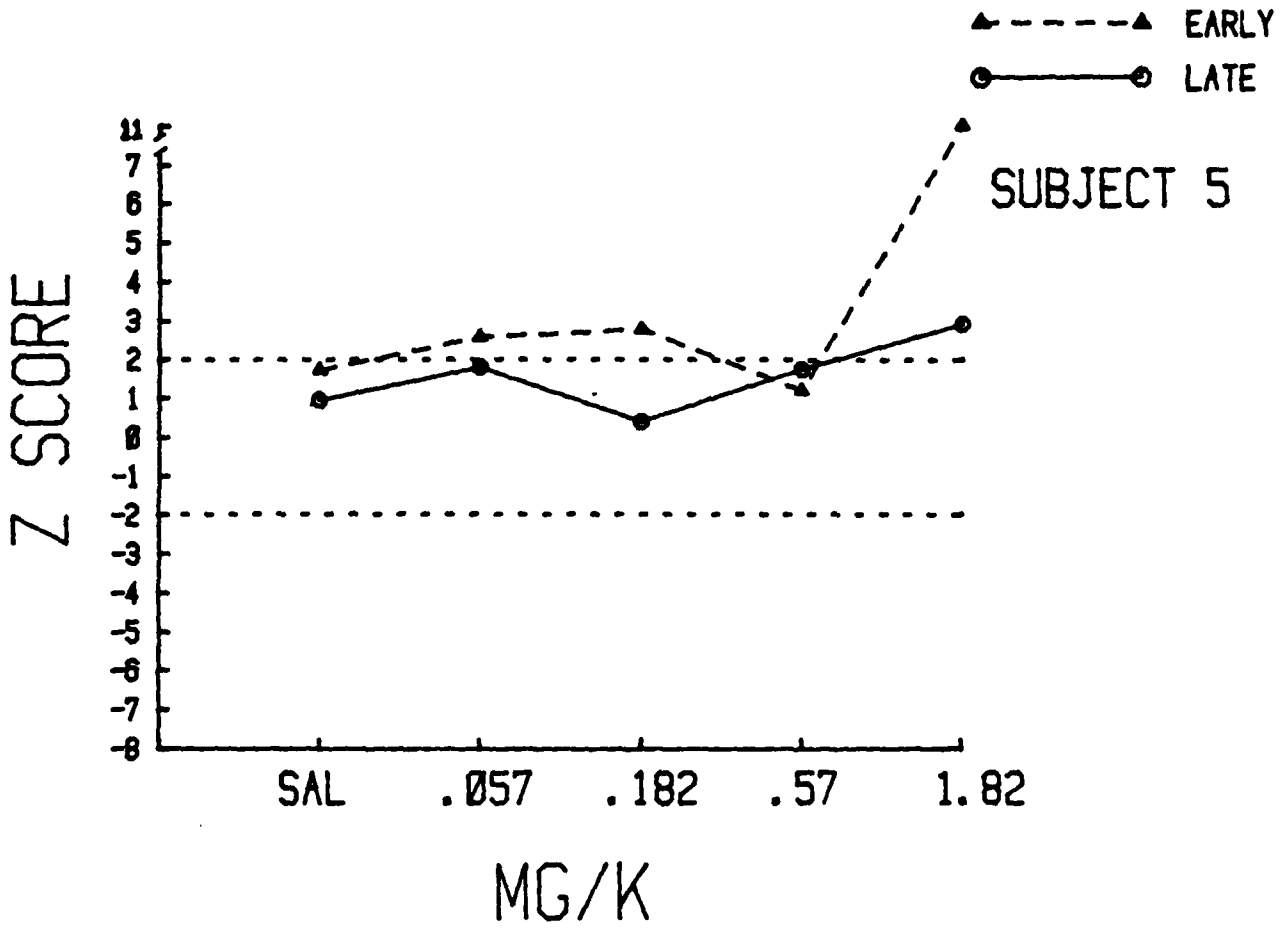

BENACTYZINE
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
SUBJECT 5
Z SCORE
11
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.057
.182
.57
1.82
MG/K

Table 6. Benactyzine

"Worst Case" Absolute Scores
Subject 4
Dose: 1.82 mg/K

	Baseline	Drug/Early	Drug/Late
Percent of trials target fixated:	98 ±1.3	*	79.6
ON SUCCESSFUL TRIALS:			
Reaction time to begin search (msec)	202 ±12	*	234
Time required to fixate target (msec)	311 ±32	*	478
Number of fixations required to fixate target	1.4 ±.11	*	1.8
Length of scan path to fixate target (radian distance in degrees of visual angle)	11.2 ±2	*	15.5
Fixation duration (msec)	712 ±51	*	493
Fixation drift (min. of arc)	15.5 ±1.3	*	19.4
Saccadic duration (msec)	30 ±1.3	*	38
Saccadic velocity (deg/sec)	157 ±96	*	224

*Failed to test

Table 7. Schedule of Completed Drug Trials

Doses: A = .57 mg/K; B = 1.82; C = 5.7;
C+ = 10.1 D = Saline; E = 18.0

Subject 1	C	A	A	D	C	B	B	D	E	E		
	c	c	c	c	c	c	c	c	c	c		
Subject 3	D	D	A	B	A	B	C	C	(E)	(E)	C+	C+
	x	x	x	x	x	x	x	x			c	c
Subject 4	B	D	C	B	A	D	A	C	C+	C+		
	c	c	c	c	c	c	c	c	c	c		

() E doses were replaced by C+ doses in accordance with instructions from the Biomedical Lab.

.57 mg/K

Neurological Symptoms: Normal

Oculomotor Competence: The polygraph record of every subject contained a dysmetria that was peculiar to this drug. It can be seen in the following figures particularly at the higher doses where its severity and frequency increased but it occurred at every dose level. The dysmetria began at 6-8 min. after injection and persisted with only slight recovery for at least one hour. It is characterized by an undershoot of the monkey's shift of gaze to the target, followed by multiple step-wise attempts to correct the undershoot.

Shifts of gaze are often subdivided into a pulse of motorneuron activity which produces the fast (saccadic) component of the shift, and a step change in activity which maintains the eye at the new point of regard (fixation). The neuroanatomy of the pulse and step are partly separable and TMB_4 affected both but affected them somewhat selectively. Under the influence of the drug the saccade and the fixation fell short of their mark, but the fixation was more hypometric than the pulse component. The saccadic pulse brought the eyes farther toward the target than the step could maintain and the fixation fell back to a shorter position as if on an elastic tether.

At this lowest dose the dysmetria was infrequent enough to not greatly affect the polygraph record or alter calculated parameters such as drift, velocity, and duration of saccades and fixations. However, the undershoot is detected in the measure that shows targeting error (distance from target of the first "on-target" fixation) to exceed normal (57 vs. 44 ± 5.6 min.).

Visual Search: Normal, except for a slight decrement during the Late session in one subject. The monkeys initiated trials without pauses and appeared motivated.

1.82 mg/K

Neurological Symptoms: Normal

Oculomotor Competence: The dysmetria already described appeared with the same frequency as at the lower dose and did not affect the calculated oculomotor parameters in any consistent way.

Visual Search: The monkeys performed briskly and none showed any decrement in the formal measures.

5.7 mg/K

Neurological Symptoms: On one of its two drug trials at this dose, subject 3 vomited 5 minutes after injection and proceeded then to test normally. No other symptoms appeared in any of the monkeys.

Oculomotor Competence: The dysmetria increased in frequency at this dose and again appeared in the analysis as increased targeting error (58 vs. 44 ± 5.6 min.).

Visual Search: Normal

10.1 mg/K

Neurological Symptoms: Subject 3 vomited again, this time on both days of the dose test. Slight ptosis was observed in both subjects and persisted through the testing period.

Oculomotor Competence: Dysmetria was quite pronounced. The monkeys needed 4-5 saccades to cover a distance normally traversed in a single saccade. Fixations within the on-target sector fell wide of the target (64 vs. 31 ± 4.6 min.). Other oculomotor parameters were abnormal. The step-wise corrective shifts of gaze introduced a number of short fixations lowering average fixation duration (400 vs. 742 ± 68 msec.). The record

shows rounded sloping fixations (drift: 33 vs. 18 ± 1.6 min.). In primates saccadic velocity increases with saccadic distance. Thus either muscle weakness or a plethora of small but normal saccades could explian the lowered average saccadic velocity (105 vs. 214 ± 11.7 deg/sec.).

Visual Search: The monkeys persevered through Early and Late sessions with only an occasional hiatus in testing. However, the graphs indicate that their performance was abnormal during the Early session. One of the two subjects (4) improved in the Late period, the other remained deficient. Typical session values for Search were

Percent of targets fixated:	74 vs. 98.6 ± 1.2
Reaction time to begin search (msec.):	257 vs. 225 ± 15
Time to find the target (msec.):	649 vs. 445 ± 37
Number of fixations to find the target:	2.2 vs. 1.75 ± .22

18.0 mg/K

Only one animal (1) received this dose. The level was then abandoned as uninformative because of its severe effect on the monkey's oculomotor and Visual Search capability.

Neurological Symptoms: Moderate ptosis, jaw and limb paresis persisted for up to 1.5 hours after injection. An occasional tremor was also noted.

Oculomotor Competence: The record was grossly ataxic. The dysmetria was accompanied by large spiking saccades that interupted fixations. All of the same oculomotor parameters were affected as reported for the 10.1 mg/K dose. In addition the range of eye movements was restricted. The monkey could no longer foveate the most eccentric targets.

Visual Search: Testing was erratic and halting. Performance was poor.

In summary, the main effect of TMB_4 was oculomotor. It caused a hypometric shift of gaze that reduced both the pulse and step components of the monkeys' shift of gaze. This drug effect began at about 8 minutes after injection and persisted with slight improvement for at least one hour.

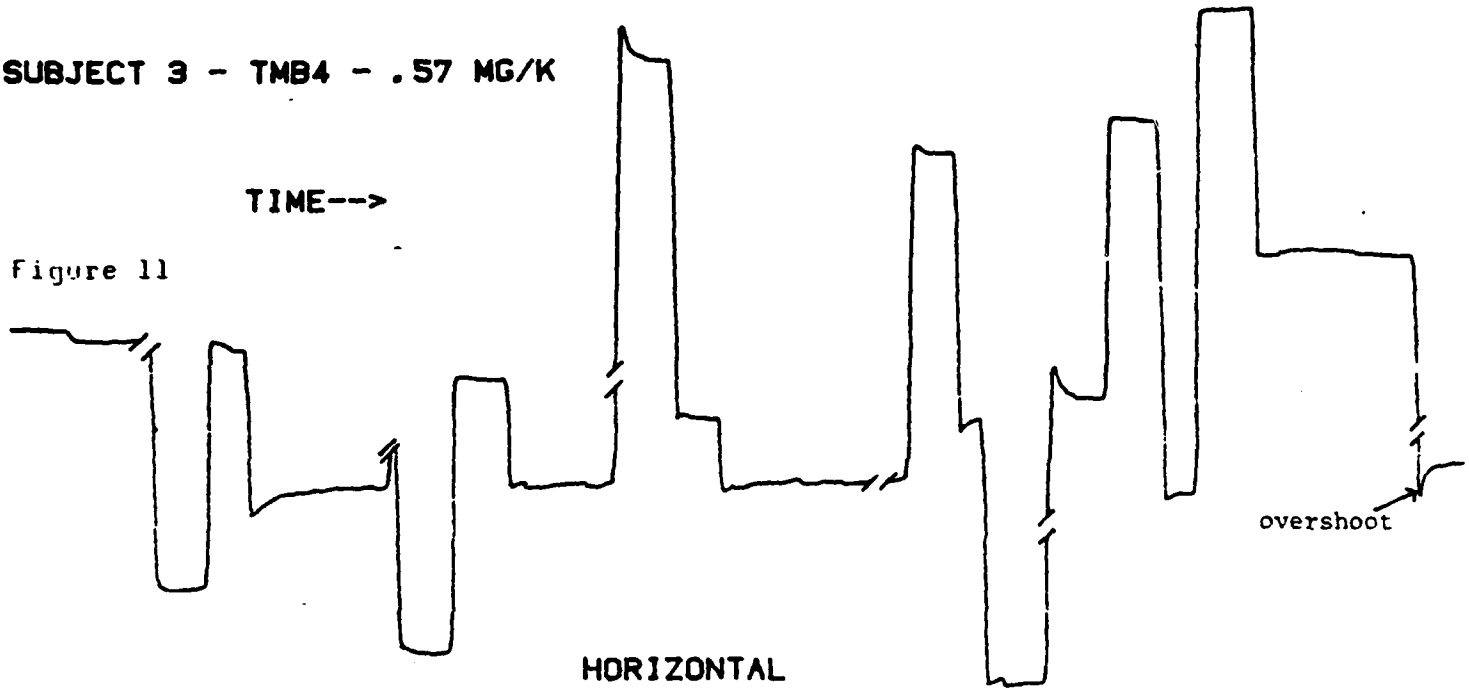
At doses below 18 mg/K the drug did not reduce motivation to test and below 10 mg/K had little effect on Visual Search. At 10 mg/K and above eye movements became so ataxic as to markedly impair the success and speed of fixating visual targets.

OCULOMOTOR RECORD - TMB4

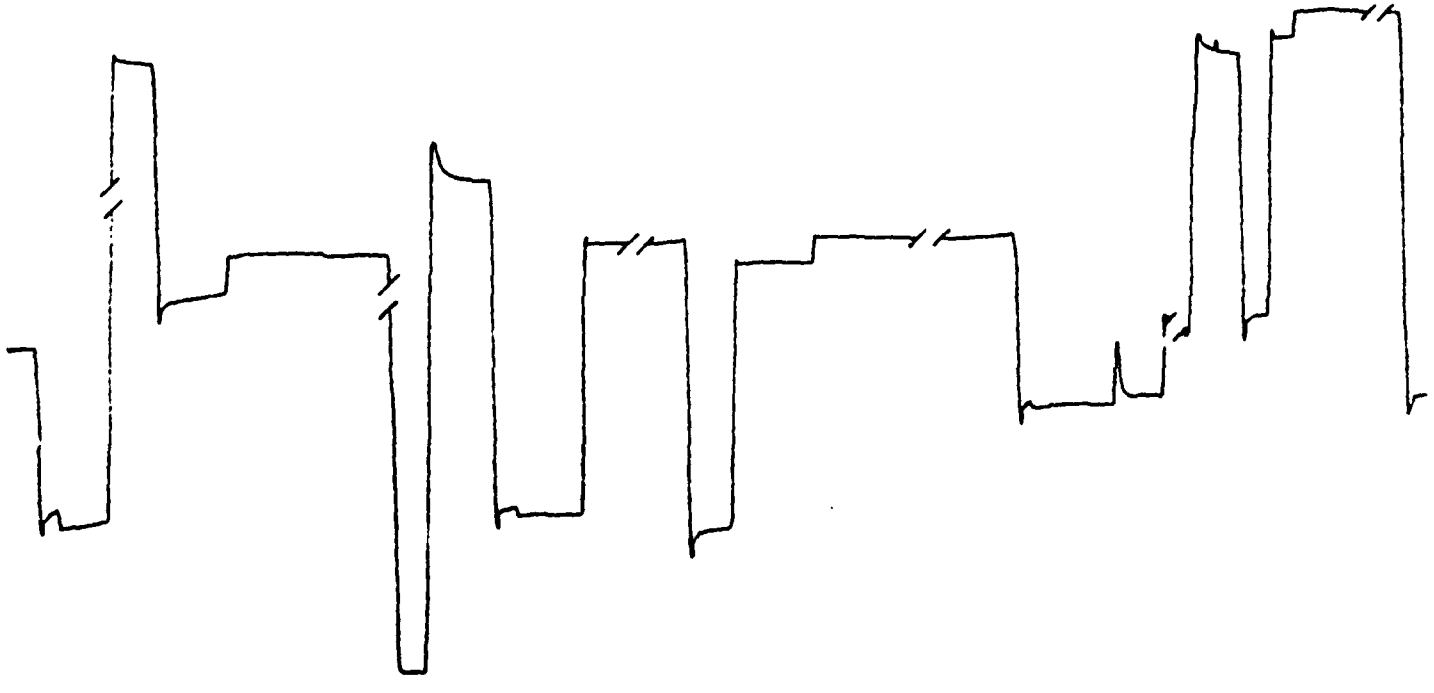
SUBJECT 3 - TMB4 - .57 MG/K

TIME-->

Figure 11

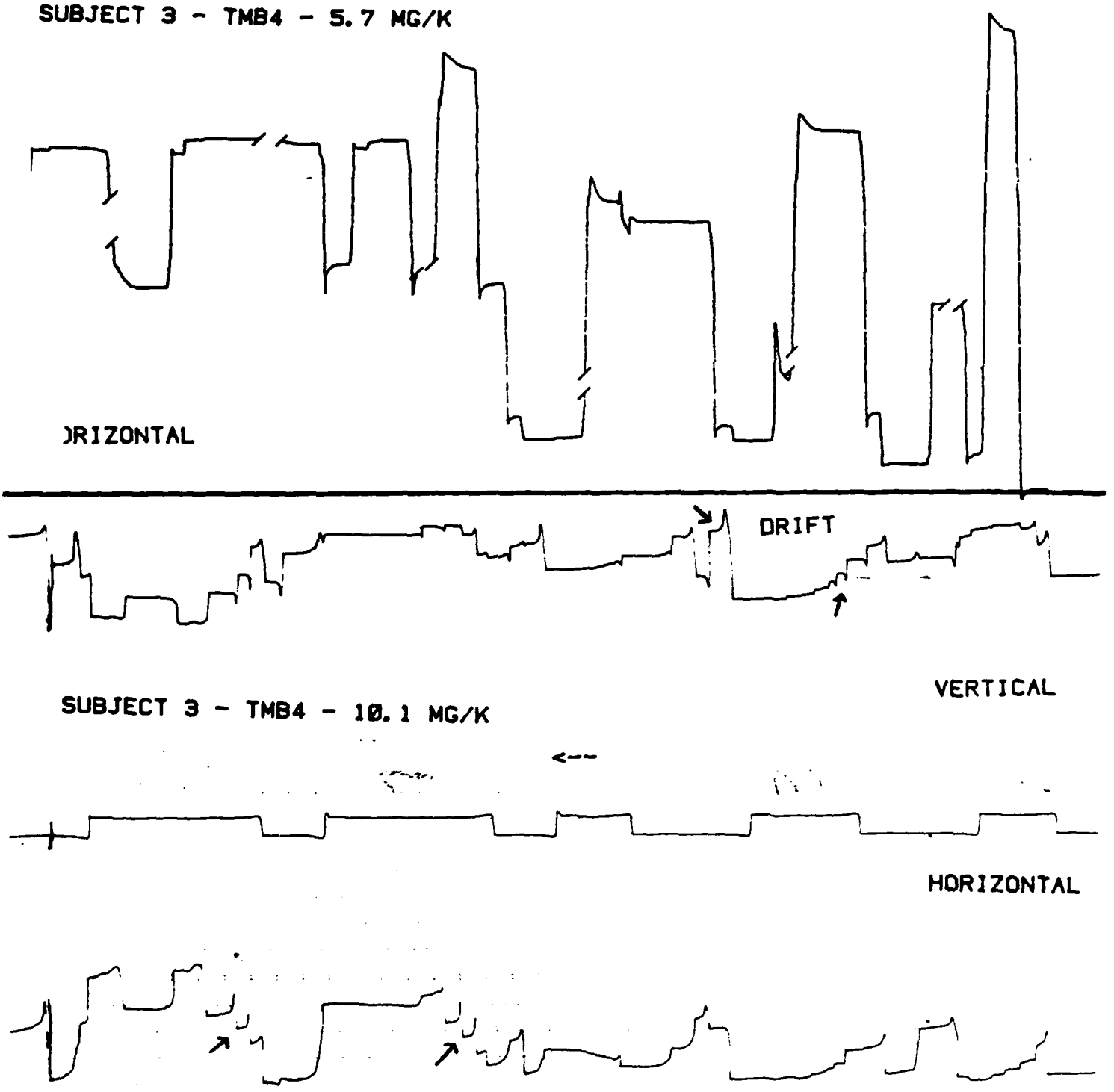


SUBJECT 3 - TMB4 - 1.82 MG/K



HORIZONTAL

//-end of trial


SUBJECT 3 - TMB4 - 5.7 MG/K
ORIZONTAL
DRIFT
VERTICAL
SUBJECT 3 - TMB4 - 10.1 MG/K
HORIZONTAL
HYPOMETRIC, STEPWISE SACCADES
18 MG/K
drift

SUBJECT 3 - TMB4 - 10.1 MG/K

RIAL = 11 TARGET = 6(F) XINC = 20.49 YINC = 25.37

00----*---10----*---20----*---30----*---40----*---50----*---60----*---70----*

Legend: Replica of viewing screen, shrunken in one dimension to fit on page.
Upper case= possible positions of target. Target appeared at F on this trial.
Lower case= position of fixations, alphabetically in sequence. TMB_4 causes undershooting, 5-7 fixations "skid" toward target instead of single saccade which would normally traverse this distance.

A

D

E

B

a

b

c

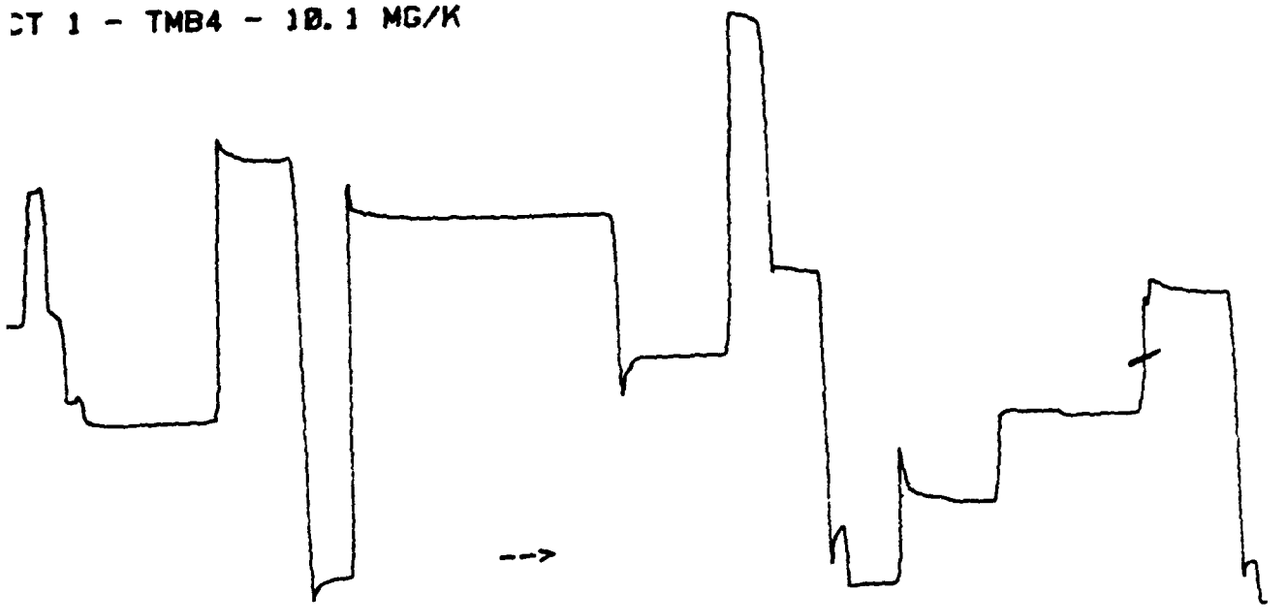
d

fF

C

f=F,

CT 1 - TMB4 - 10.1 MG/K



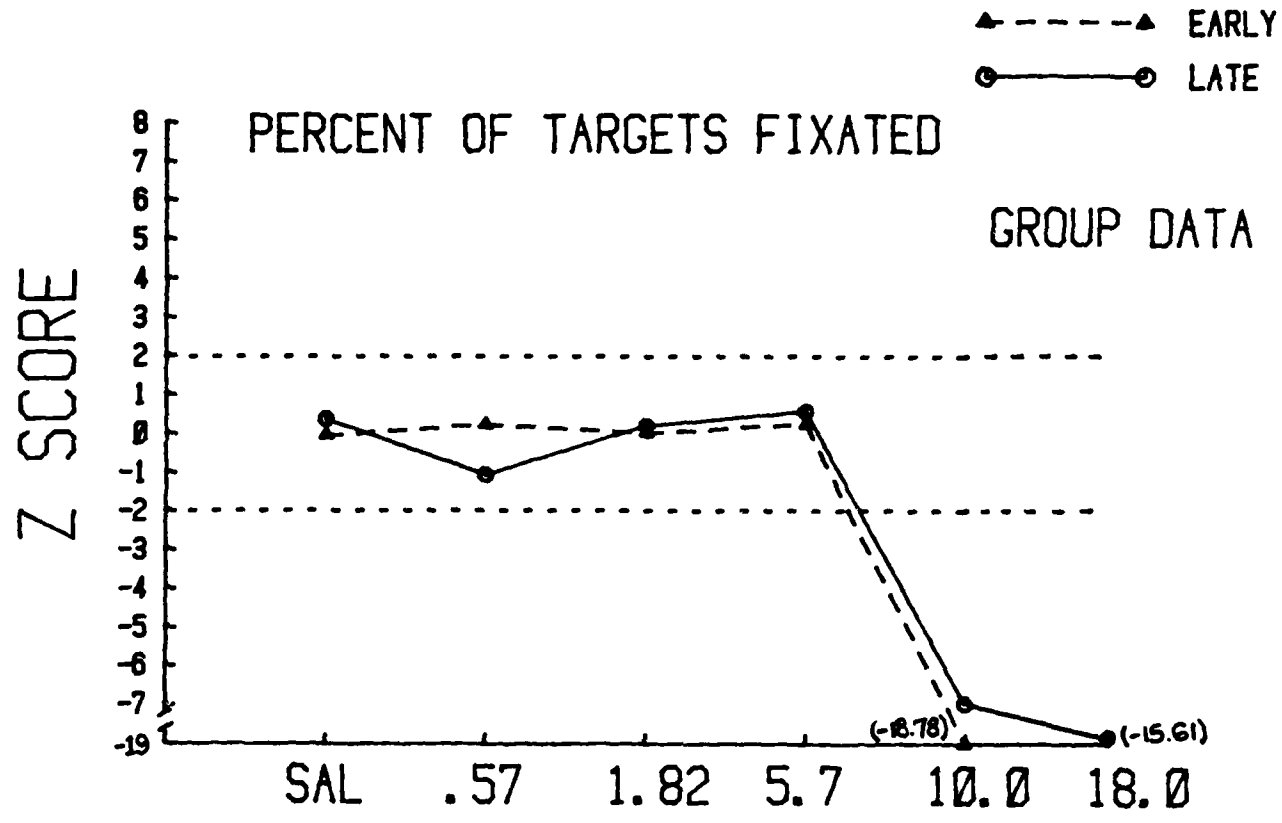
CONTAL

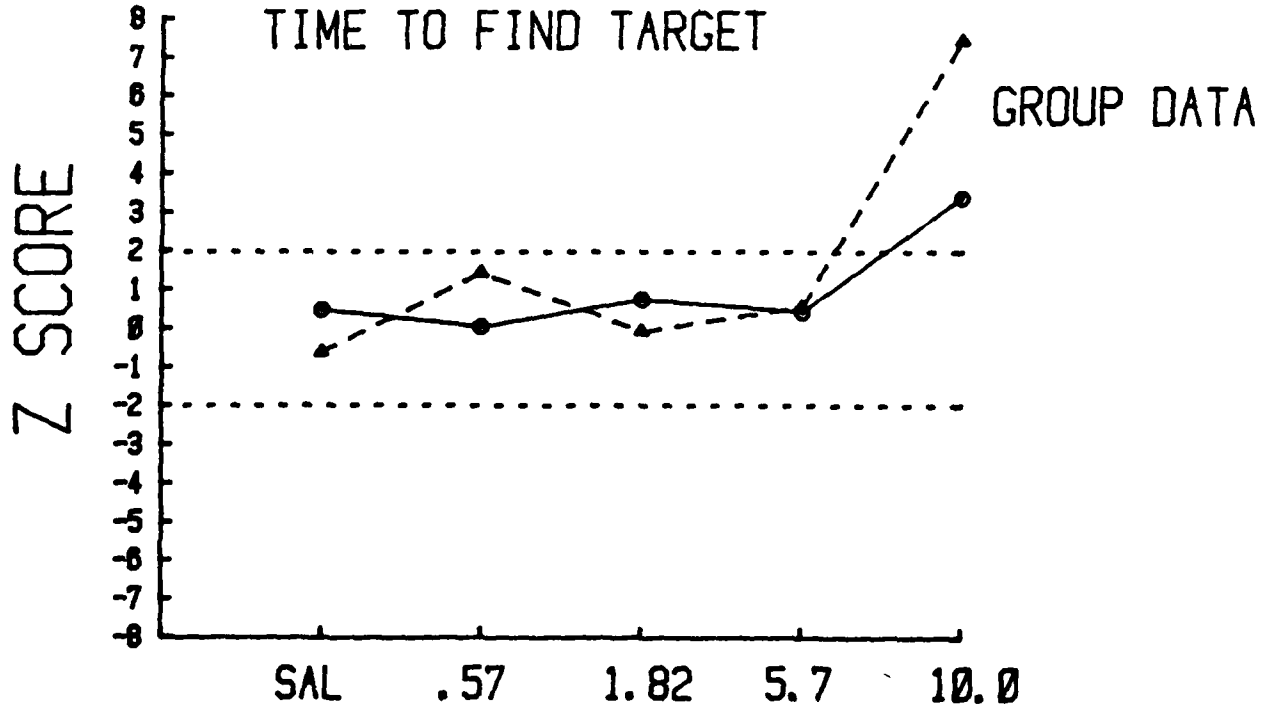
ECT 1 - TMB4 - 18 MG/K

ONTAL

Figure 12

TMB4





MG/K

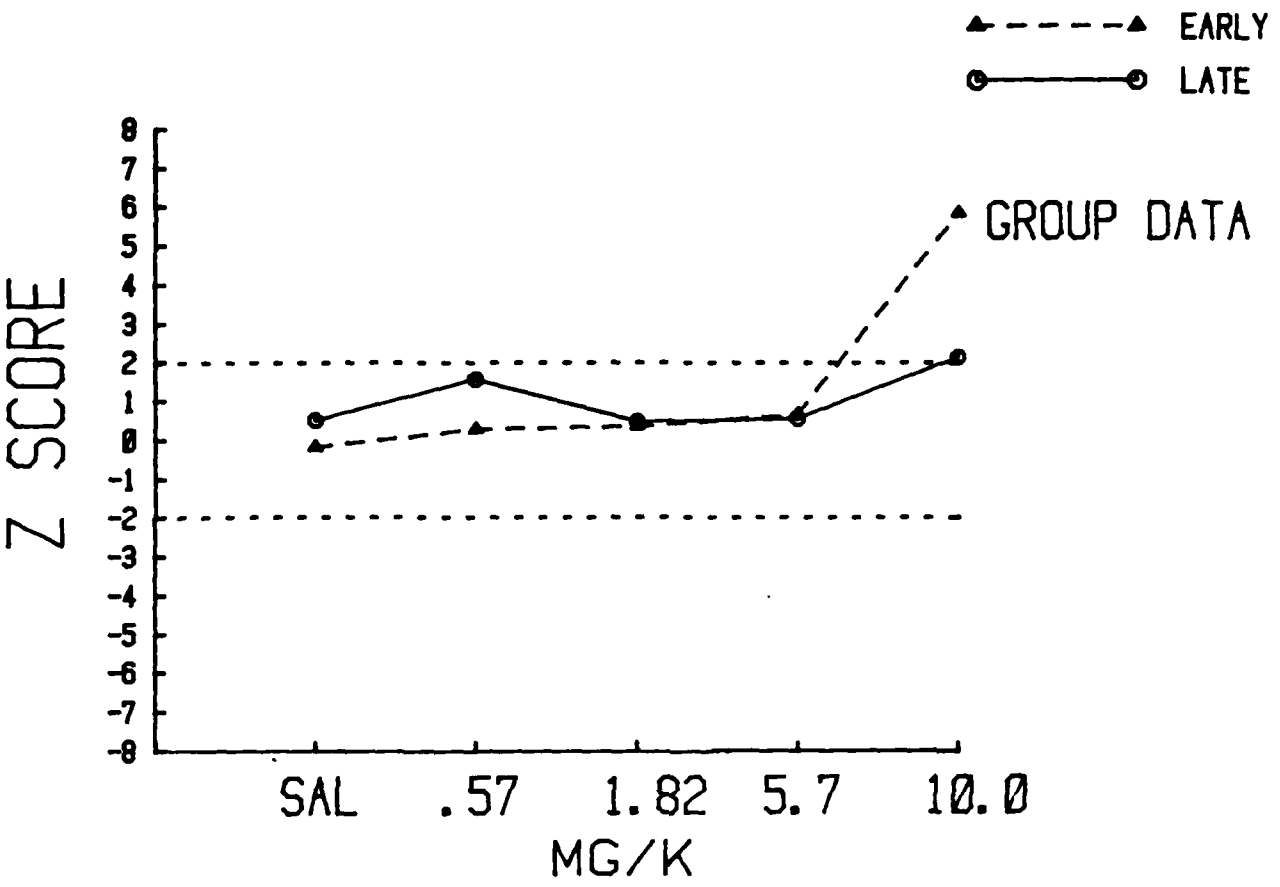
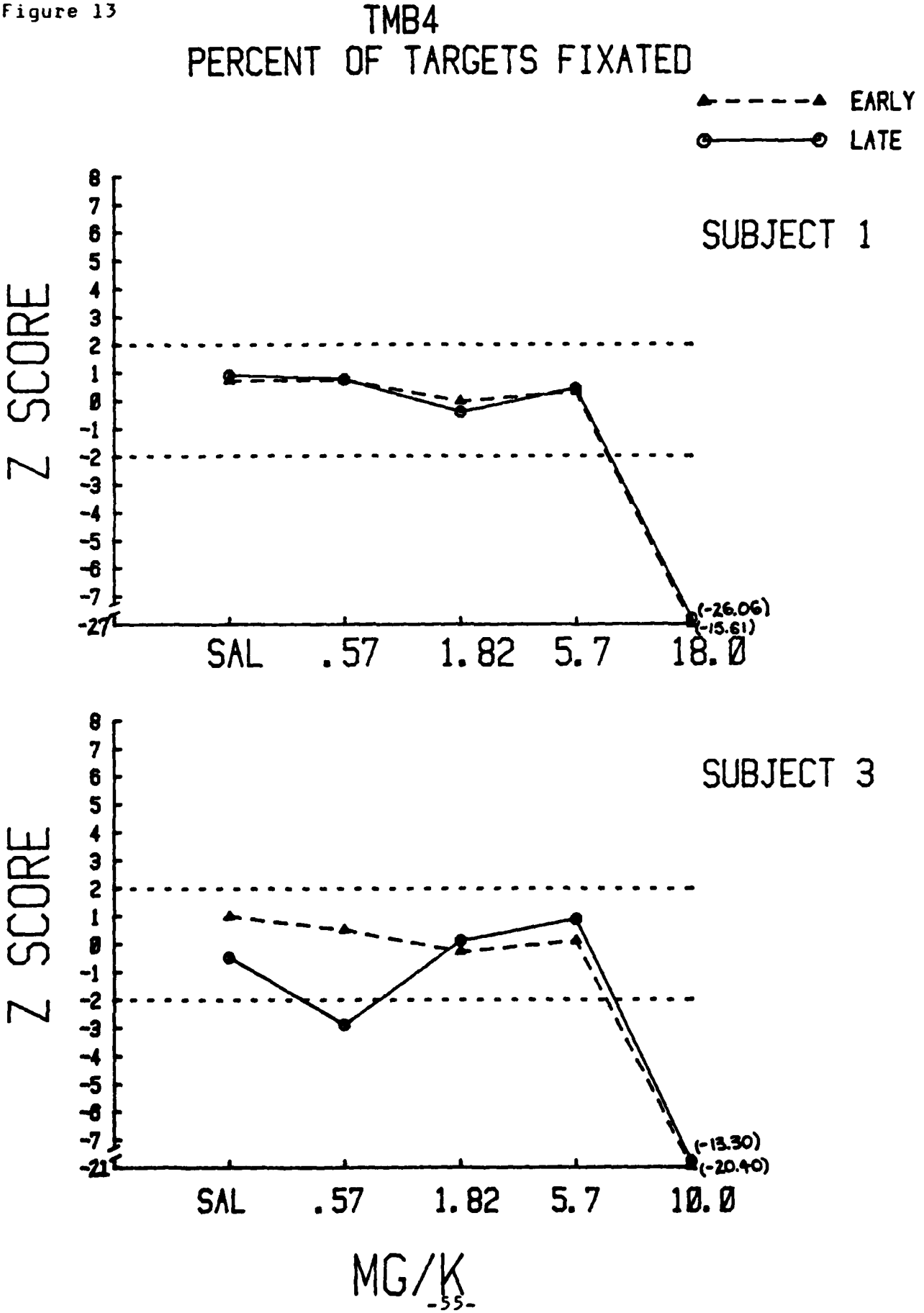
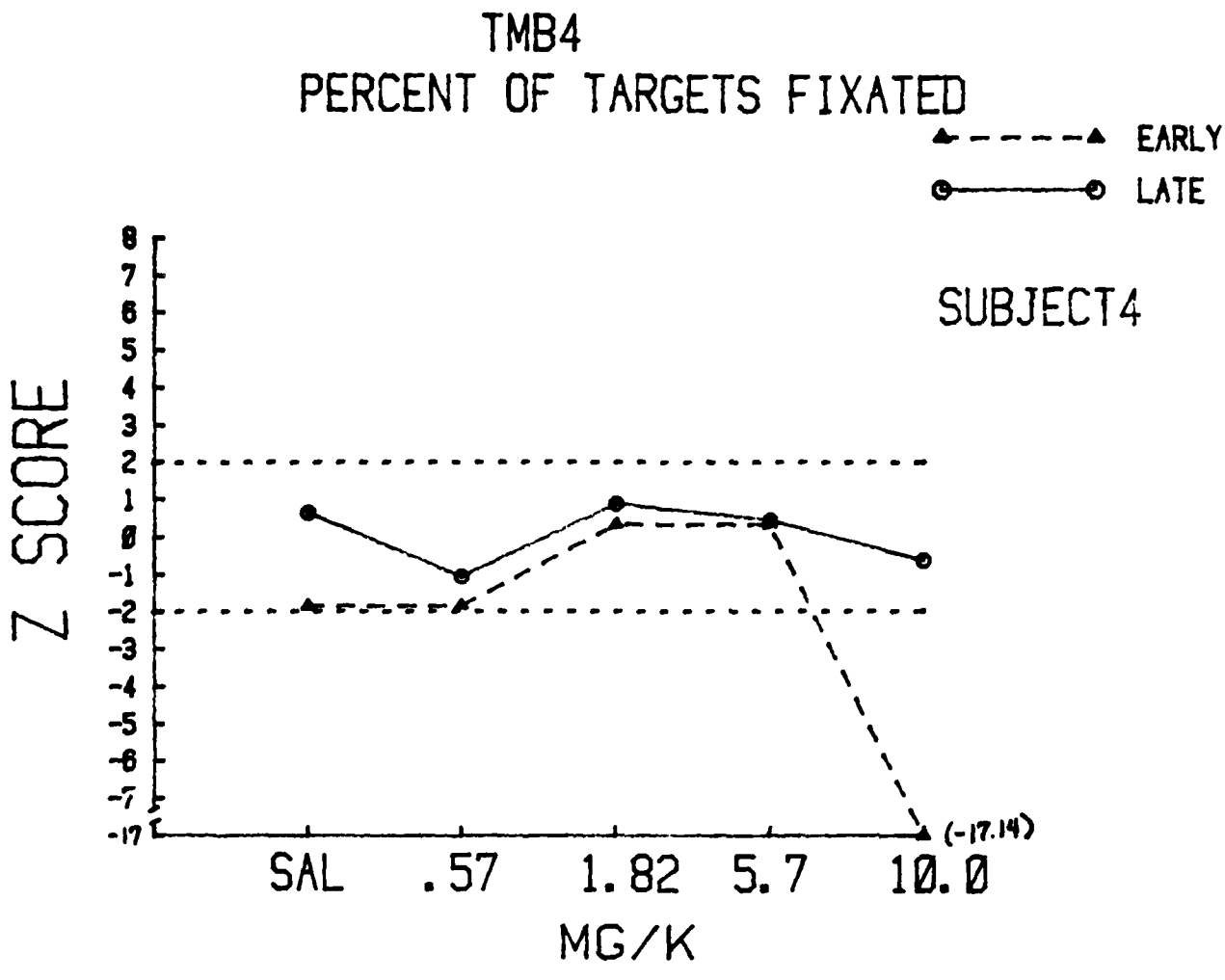
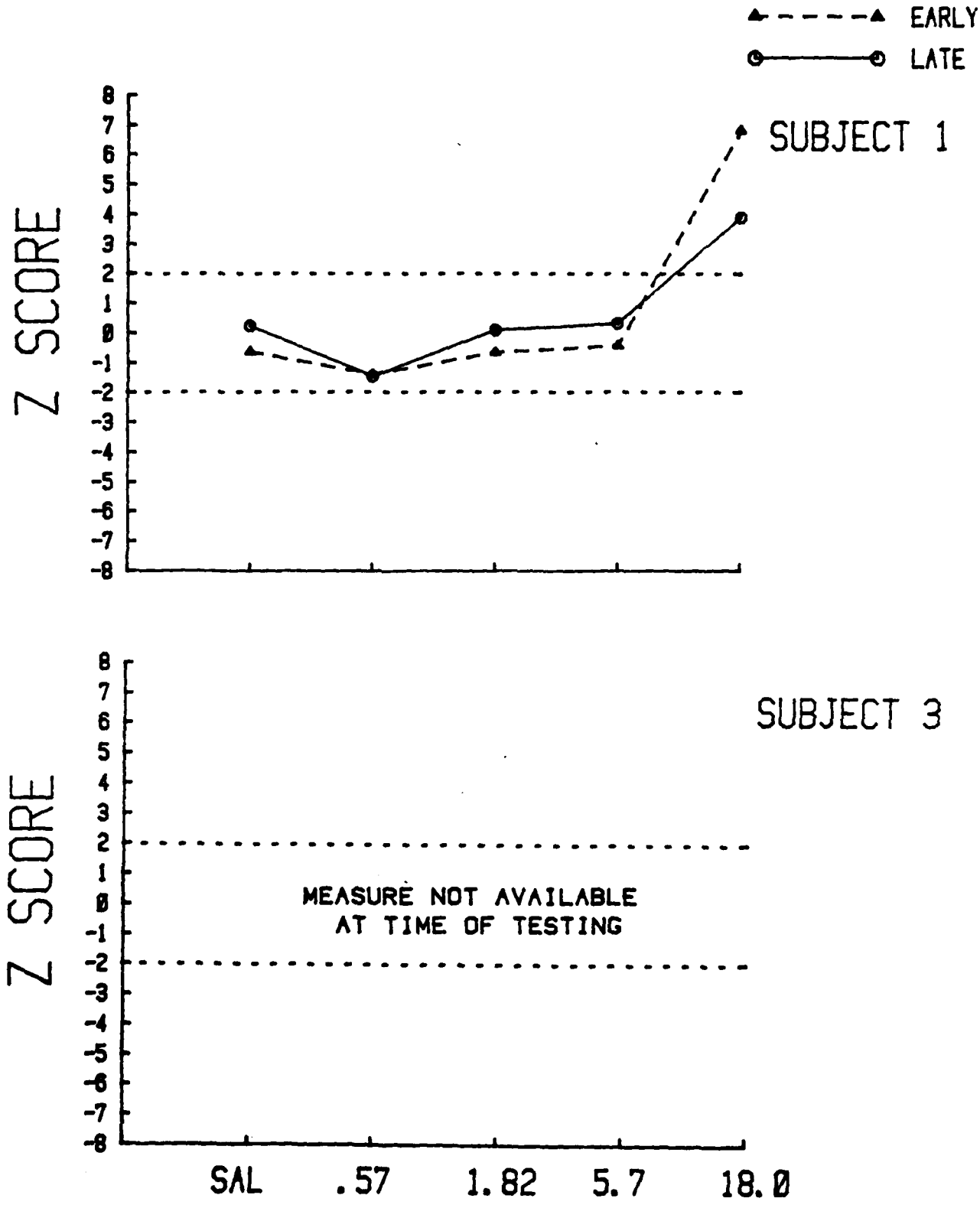

TMB4
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.57
1.82
5.7
10.0
MG/K

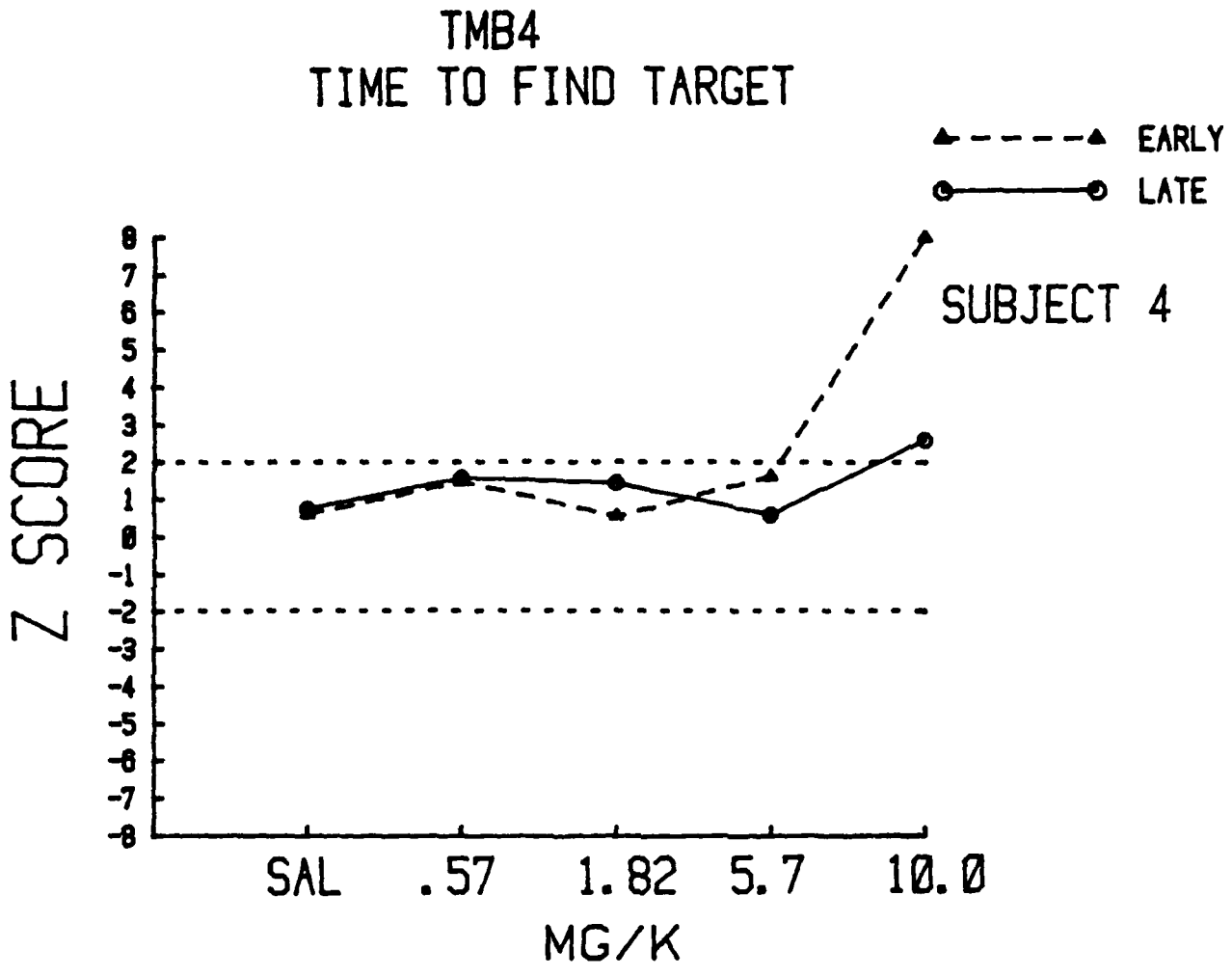
Figure 13


TMB4
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 1
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-27
(-26.06)
(-15.61)
SAL
.57
1.82
5.7
18.0
SUBJECT 3
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-21
(-13.30)
(-20.40)
SAL
.57
1.82
5.7
10.0
MG/K

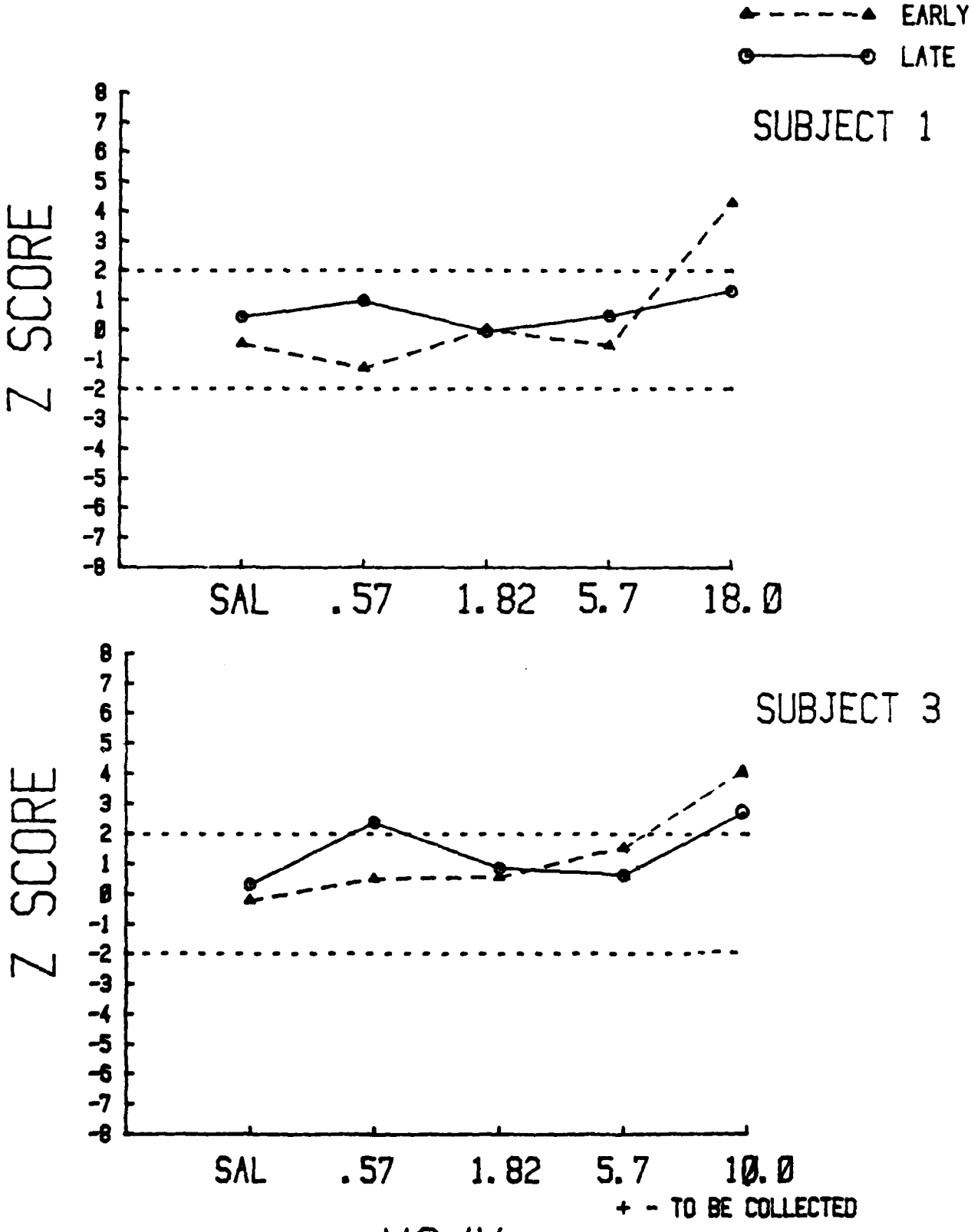

TMB4
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT4
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-17
(-17.14)
SAL
.57
1.82
5.7
10.0
MG/K

TMB4
TIME TO FIND TARGET




TMB4
TIME TO FIND TARGET
EARLY
LATE
SUBJECT 4
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.57
1.82
5.7
10.0
MG/K

TMB4
NUMBER OF FIXATIONS TO FIND TARGET



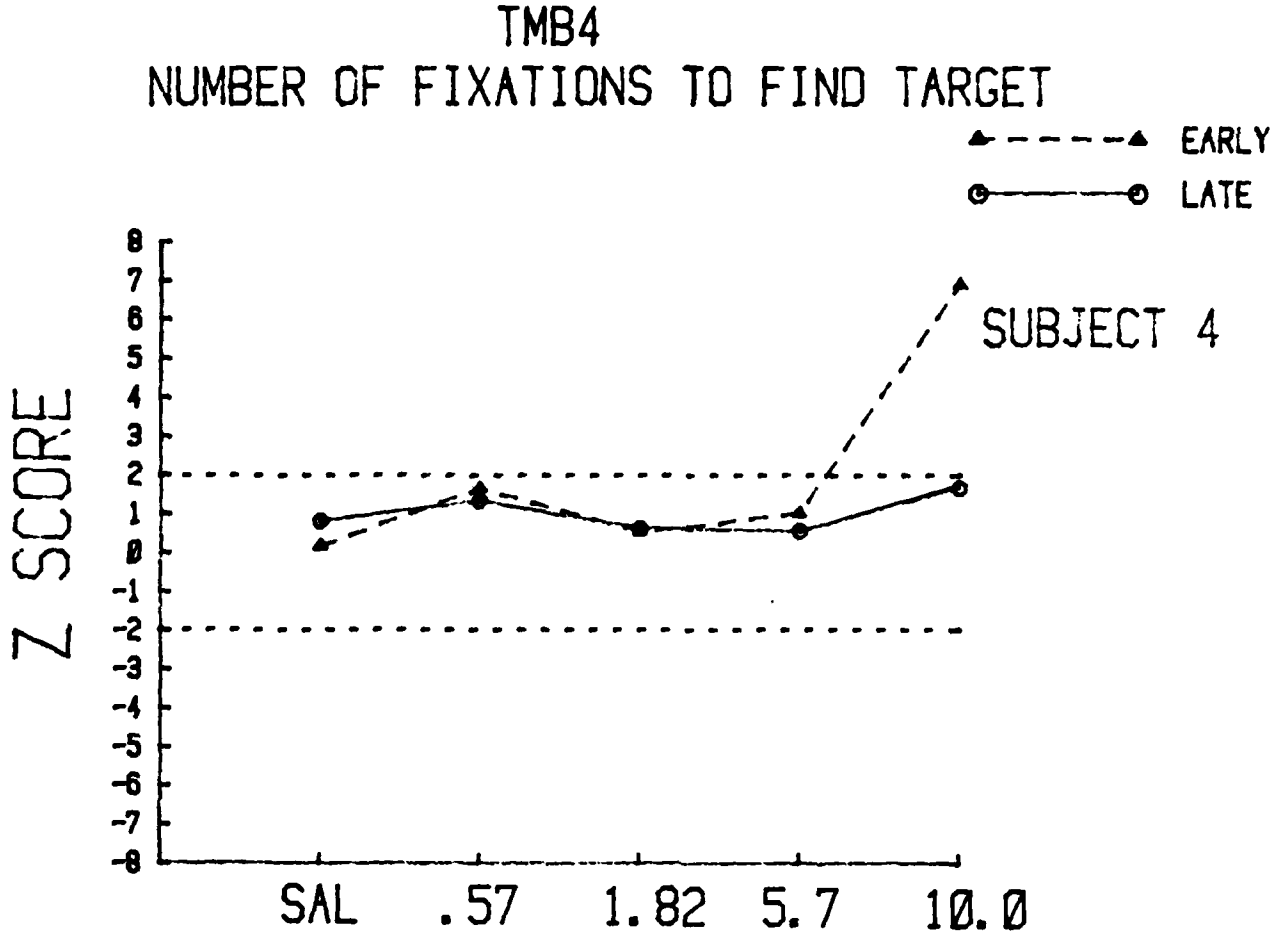

TMB4
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
SUBJECT 4
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.57
1.82
5.7
10.0

Table 8. TMB_4

"Worst Case" Absolute Scores
Subject 1
Dose: 18.0 mg/K

	Baseline	Drug/Early	Drug/Late
Percent of targets fixated	96 ±2.9	21.3	26.8
ON SUCCESSFUL TRIALS:			
Fixation drift (min. of arc)	35.4 ±2.8	47.7	41.3
Saccadic velocity (deg/sec)	178.8 ±17.6	63.6	71.2
Saccadic Duration (msec)	29.2 ±4.5	38.2	34.4
Reaction time to begin search (msec)	293 ±27	355	350
Time required to fixate target (msec)	465 ±47	784	661
Number of fixations required to fixate target	1.49 ±.14	2.1	1.7
Length of scan path to fixate target (radian distance in degrees of visual angle)	15.9 ±2.7	6.6*	6.2*

*Subject could fixate only those targets that coincidentally appeared near its point of gaze, thus leading to an artificially small scan path measure.

PHYSOSTIGMINE

Table 9. Schedule of Completed Drug Trials

Doses: A = .025 mg/K; B = .050; C = .075; D = Saline

Subject 1	A	D	C	A	B	B	A	C	D
	c	c	c	#	c	c	c	c	c
Subject 3	C	A	A	D	D	C	B	B	D
	c	c	c	c	#	c	c	c	c

Since physostigmine trials were completed on only two rhesus the summary below should be considered preliminary. Further trials of the drug with a new battery of monkeys are currently in progress.

.025 mg/K

Neurological Symptoms: Normal

Oculomotor Competence: By visual inspection the record appeared normal. This was generally confirmed by the analysis except for a slight increase in drift and targeting error.

Visual Search: At every dose physostigmine disrupted testing. The effect seemed motivational - the monkeys refused to press the lever or scan the screen, and occasionally refused to drink a free juice reward. On the trials when searching did occur, it appeared competent.

At this lowest dose the disruption was intermittent. In the Early session only one of the two subjects stopped testing. In the Late session both animals halted on the first drug test day but were little affected on the second test of this dose.

The graphs indicate a deficit on the saline trials. This has no ready explanation but was attributable to a single session with one subject. To rule out a more general sensitization to injections we compared the baseline days on which the monkeys received a saline injection and compared it to performance on the other baseline days. This analysis was repeated for every drug and did not show any "saline effect." The Z scores of the analysis for physostigmine is shown in Table 10.

Table 10. Saline Baseline Days Compared to Other Baseline Days

	Z
Percent of Targets Fixated	.40
Time To Find Targets	.31
Number of Fixations To Find Targets	.36

Thus no general sensitization to injection appeared and the single abnormal Saline session remains an unexplained anomaly.

.050 mg/K

Neurological Symptoms: Normal, with only a suspicion of mydriasis and muscle weakness.

Oculomotor Competence: Spikes appeared in the record in both subjects. They were of large amplitude, were confined to the vertical channel and recovered during the Late session in Subject 3; in the case of Subject 1, they were smaller, showed up in both channels and persisted through both sessions. Fixation drift (20 vs. 17 ± 1 min.) and targeting error (44 vs. 34 ± 4.9 min.) were abnormal. These changes improved slightly but remained elevated during the Late session.

Visual Search: Again, the most pronounced effect of the drug was to disrupt testing, and perhaps for motivational reasons to decrease the number of successful trials. On successful trials search was fairly competent except that time to find the target was slowed somewhat. The slowing was partly due to an increased reaction time to begin search after the stimuli appeared (422 vs. 302 ± 35 msec.).

.075 mg/K

Neurological Symptoms: Clear but not severe muscle weakness was diagnosed in both Early and Late sessions.

Oculomotor Competence: The records are essentially similar to those collected at the .050 mg/K dose. Spikes appeared as before and in addition small transients gave the fixations a ragged appearance. Drift and targeting error were again elevated but at this dose saccades were also slowed and markedly prolonged (Table 11).

Visual Search: Testing was disrupted through both sessions. The monkeys avoided the lever and refused orangeade. Surprisingly and perhaps out of habit, they were occasionally willing to fixate targets when we triggered the stimuli. The rate of successful trials dropped markedly but on successful trials search was surprisingly competent given their poor cooperation.

In summary, physostigmine administered to just two subjects, disrupted testing at every dose. The most notable oculomotor changes were spiking transients and at higher doses slowed velocity. However, eye movements were never severly distorted. The monkeys' failure to find the targets was probably a motivational problem since on occasional trials their searching was slightly slowed but not markedly abnormal.

OCULOMOTOR RECORD - PHYSOSTIGMINE

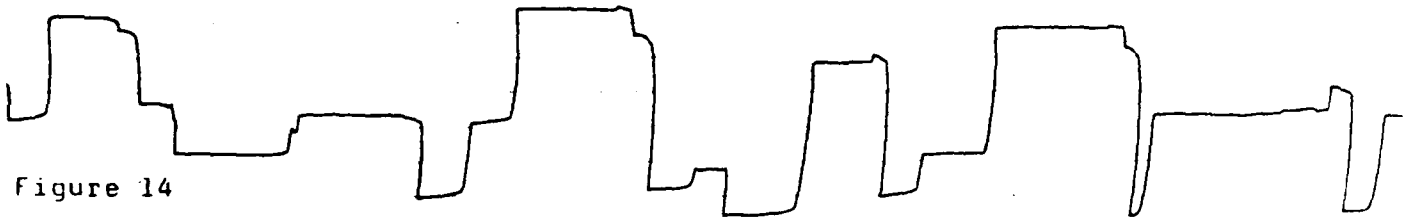
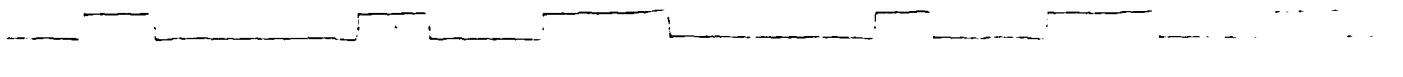


Figure 14

SUBJECT 1 - BASELINE

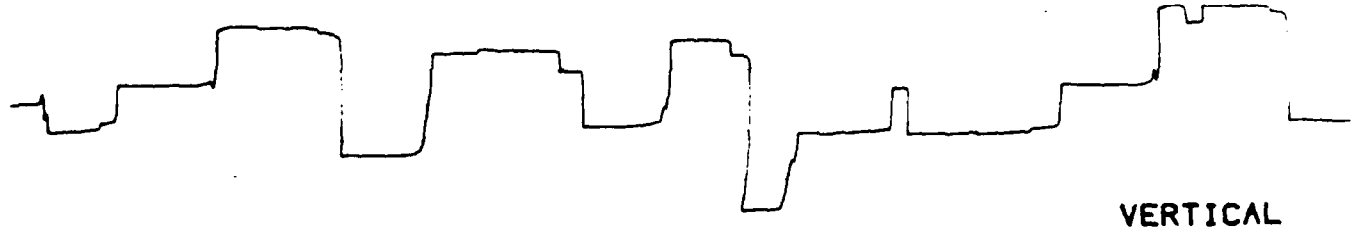
VERTICAL



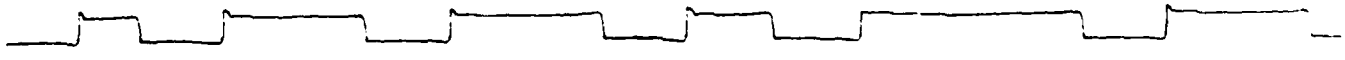
<--

HORIZONTAL

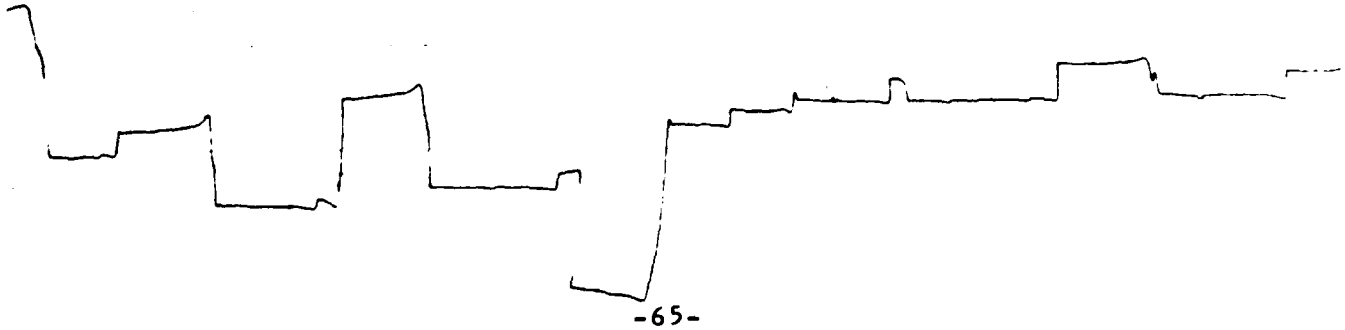
SUBJECT 1 - PHYSOSTIGMINE - .025 MG/K



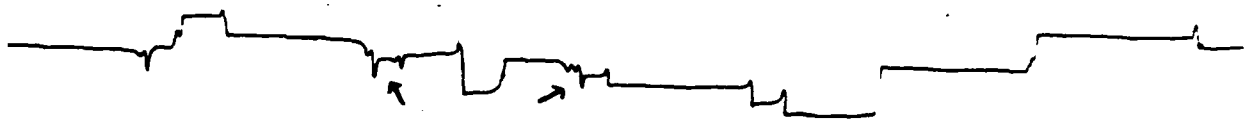
VERTICAL



HORIZONTAL



SUBJECT 1 - PHYSOSTIGMINE - .050 MG/K

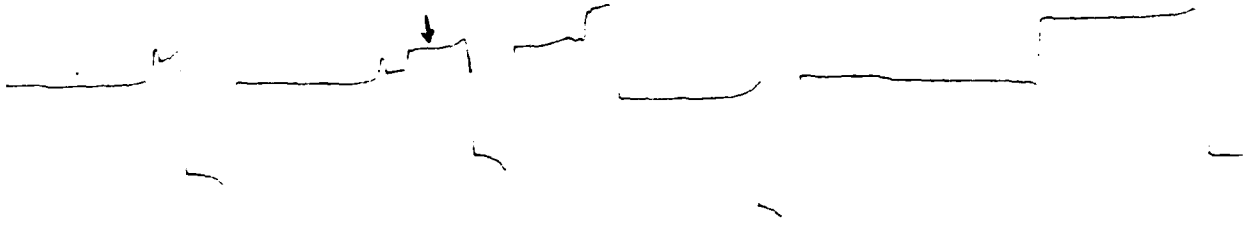


SPIKES

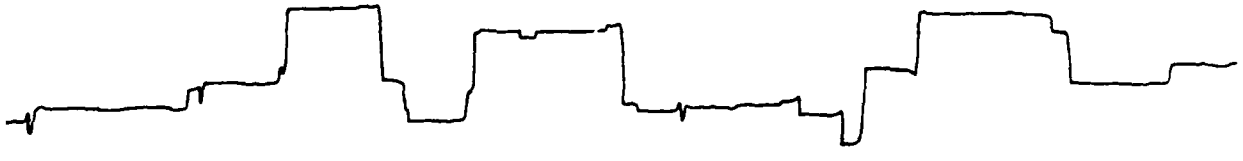
VERTICAL

HORIZONTAL

DRIFT



SUBJECT 1 - PHYSOSTIGMINE - .075 MG/K

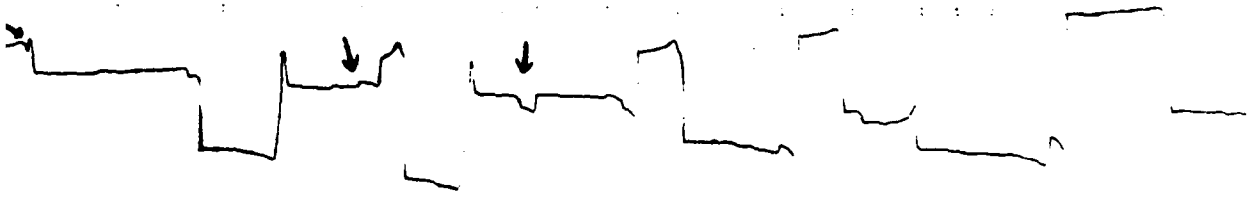


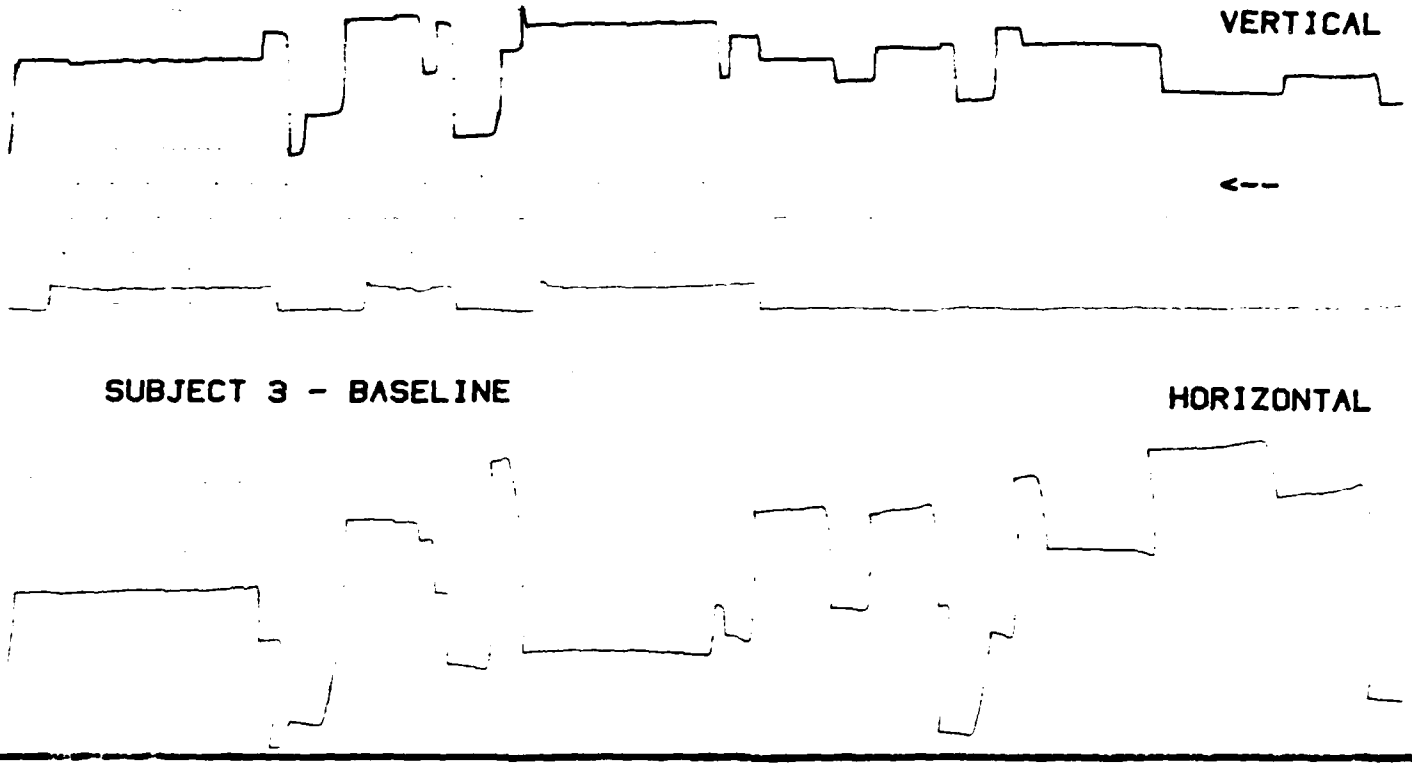
VERTICAL

HORIZONTAL

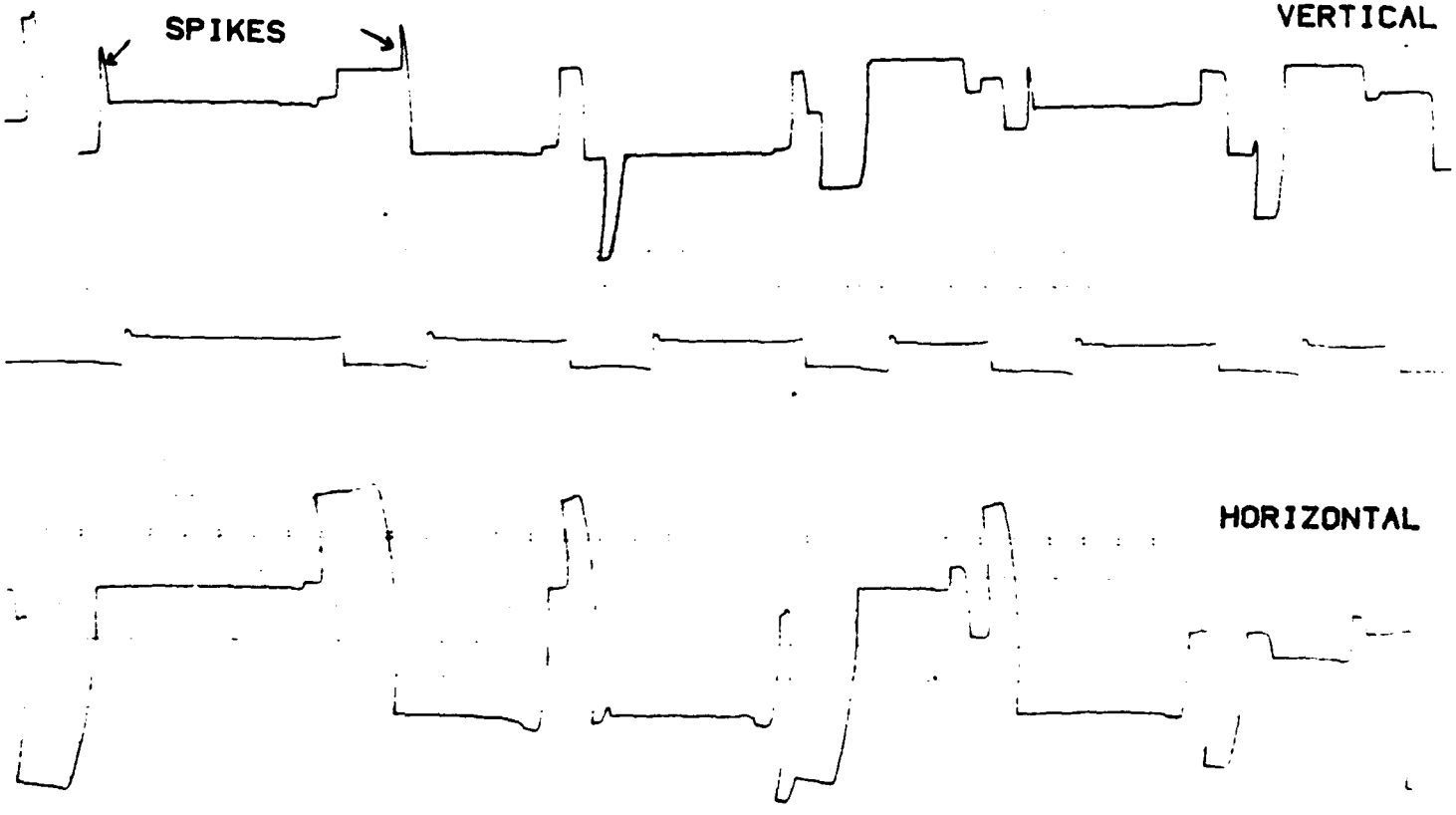
SPIKES

FRACTURED FIXATION

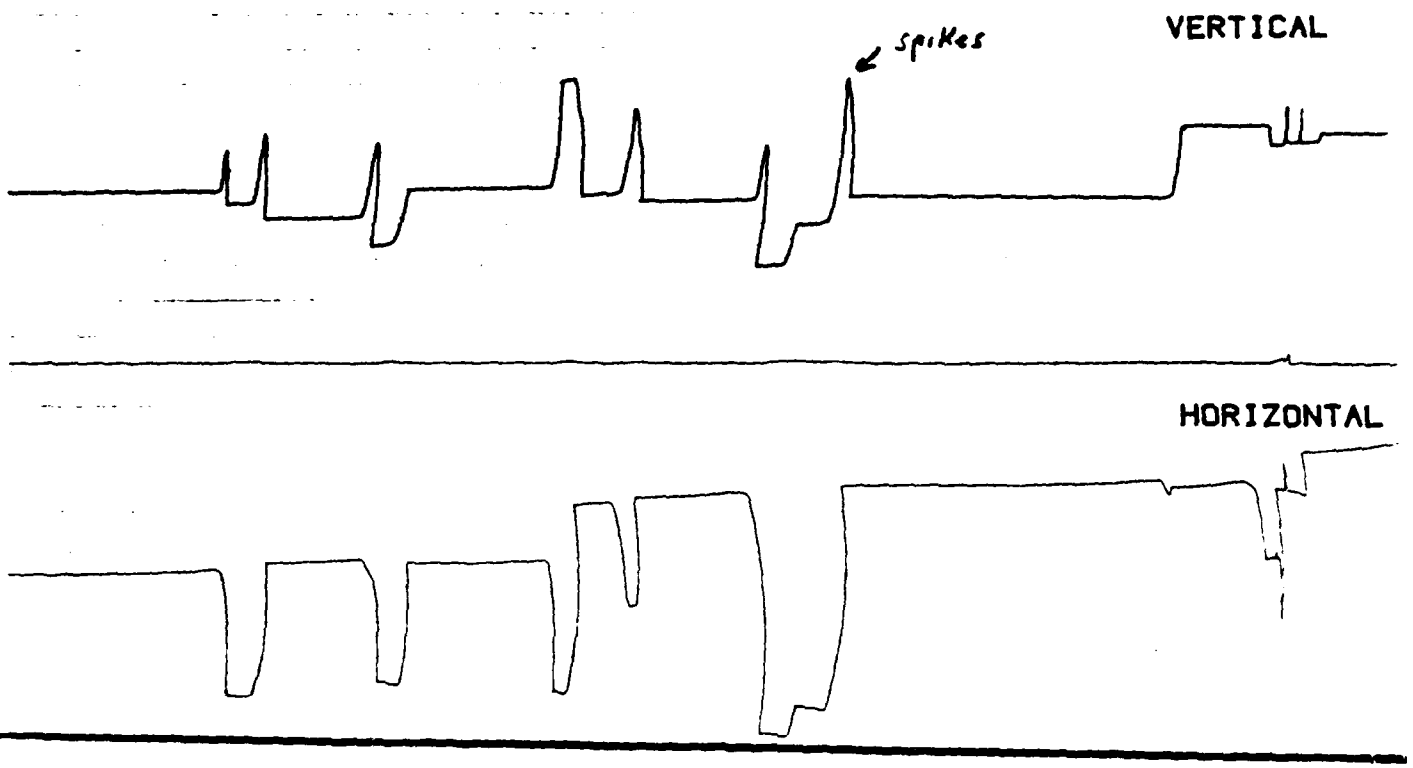




SUBJECT 3 - PHYSOSTIGMINE - .025 MG/K



SUBJECT 3 - PHYSOSTIGMINE - .050 MG/K



SUBJECT 3 - PHYSOSTIGMINE - .075 MG/K

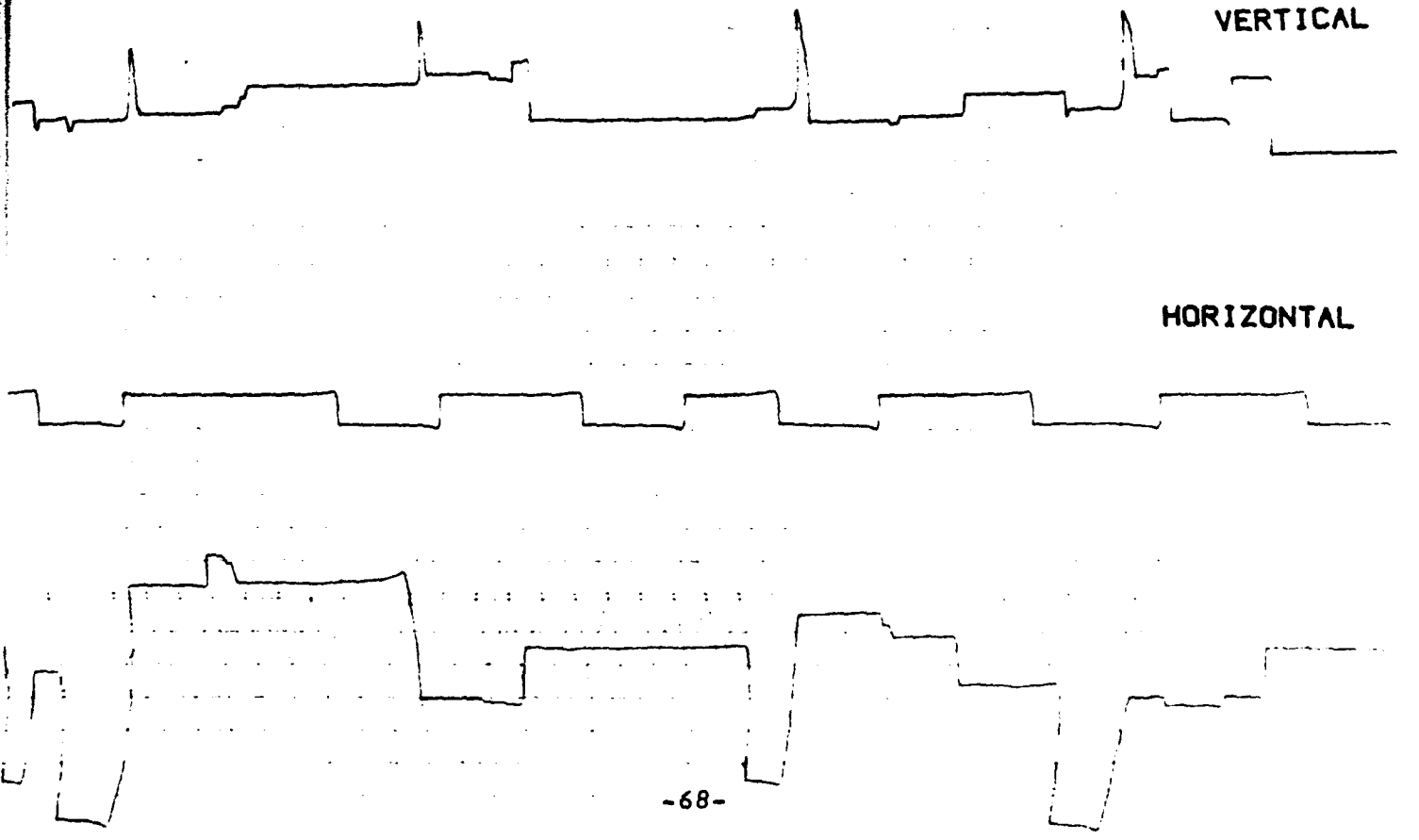
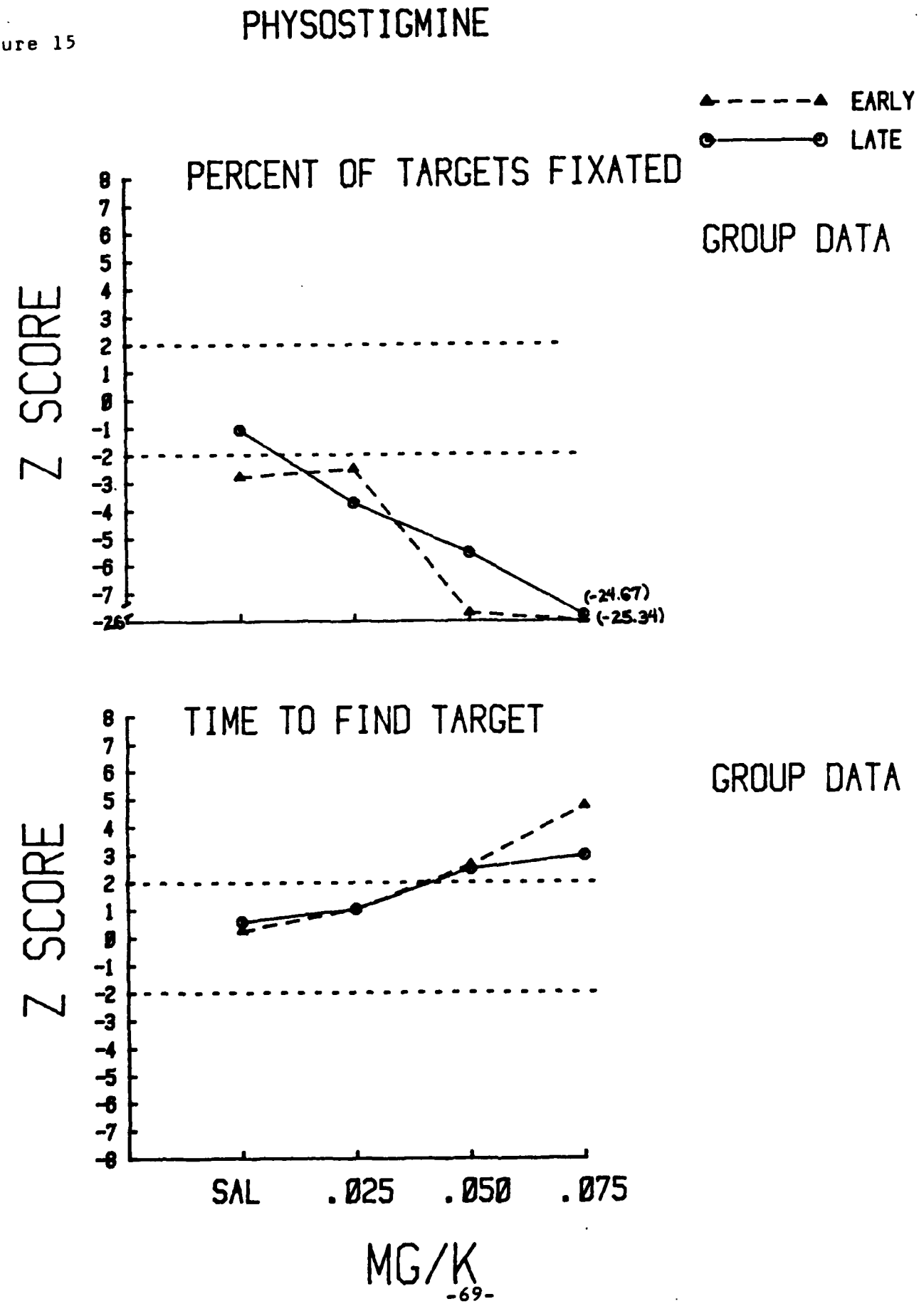


Figure 15


PHYSOSTIGMINE
EARLY
LATE
PERCENT OF TARGETS FIXATED
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-26
(-24.67)
(-25.34)
TIME TO FIND TARGET
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.025
.050
.075
MG/K

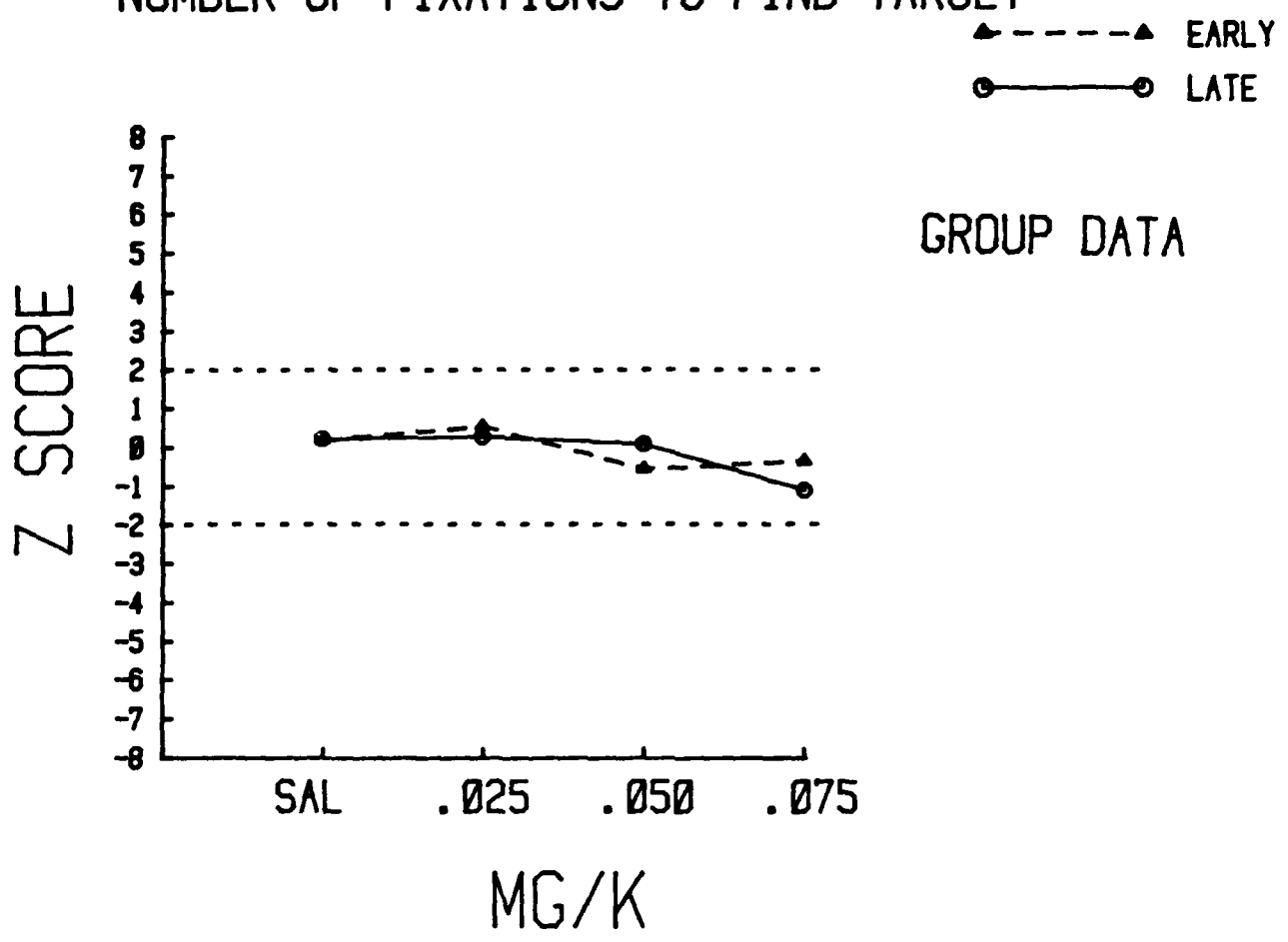
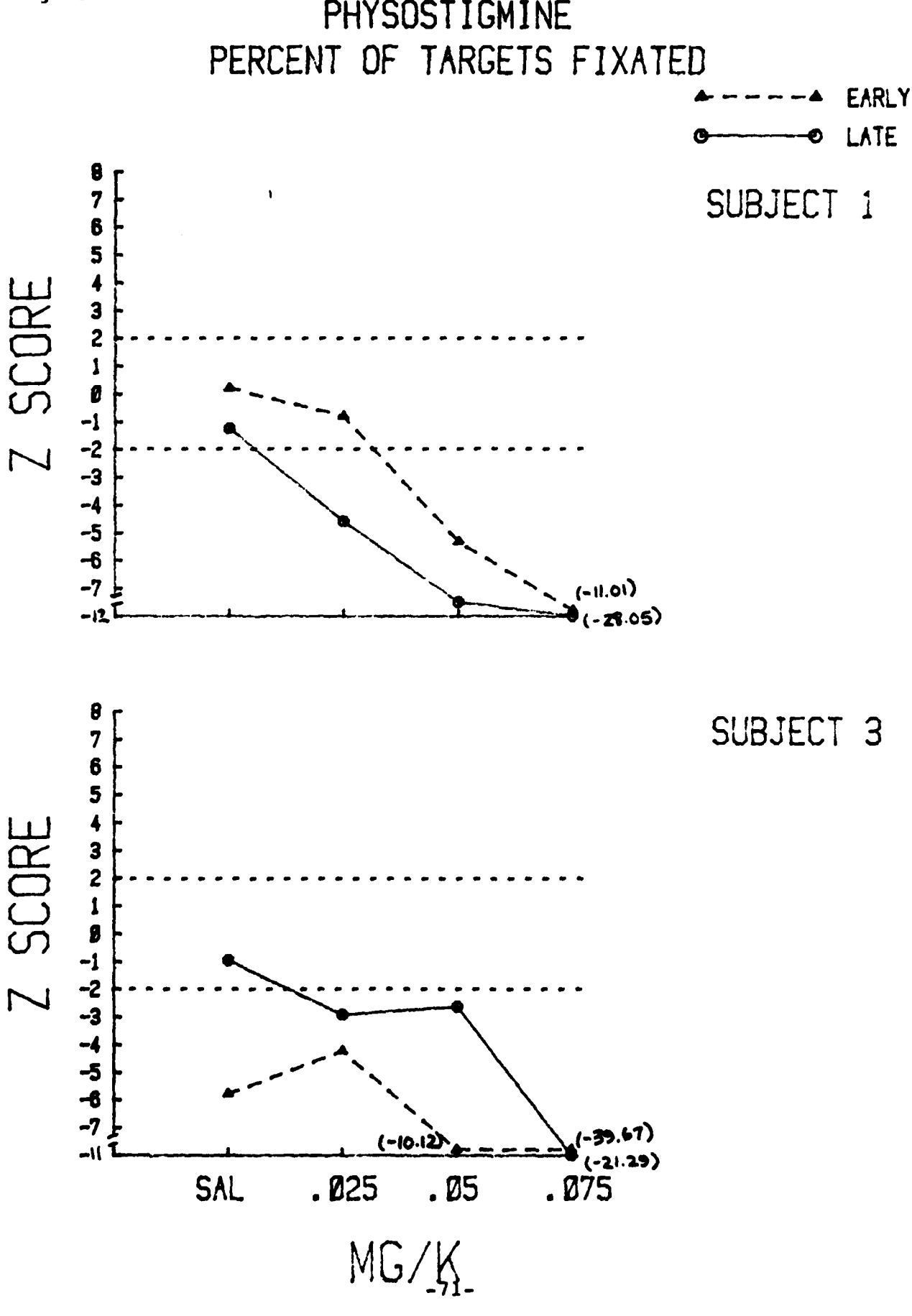
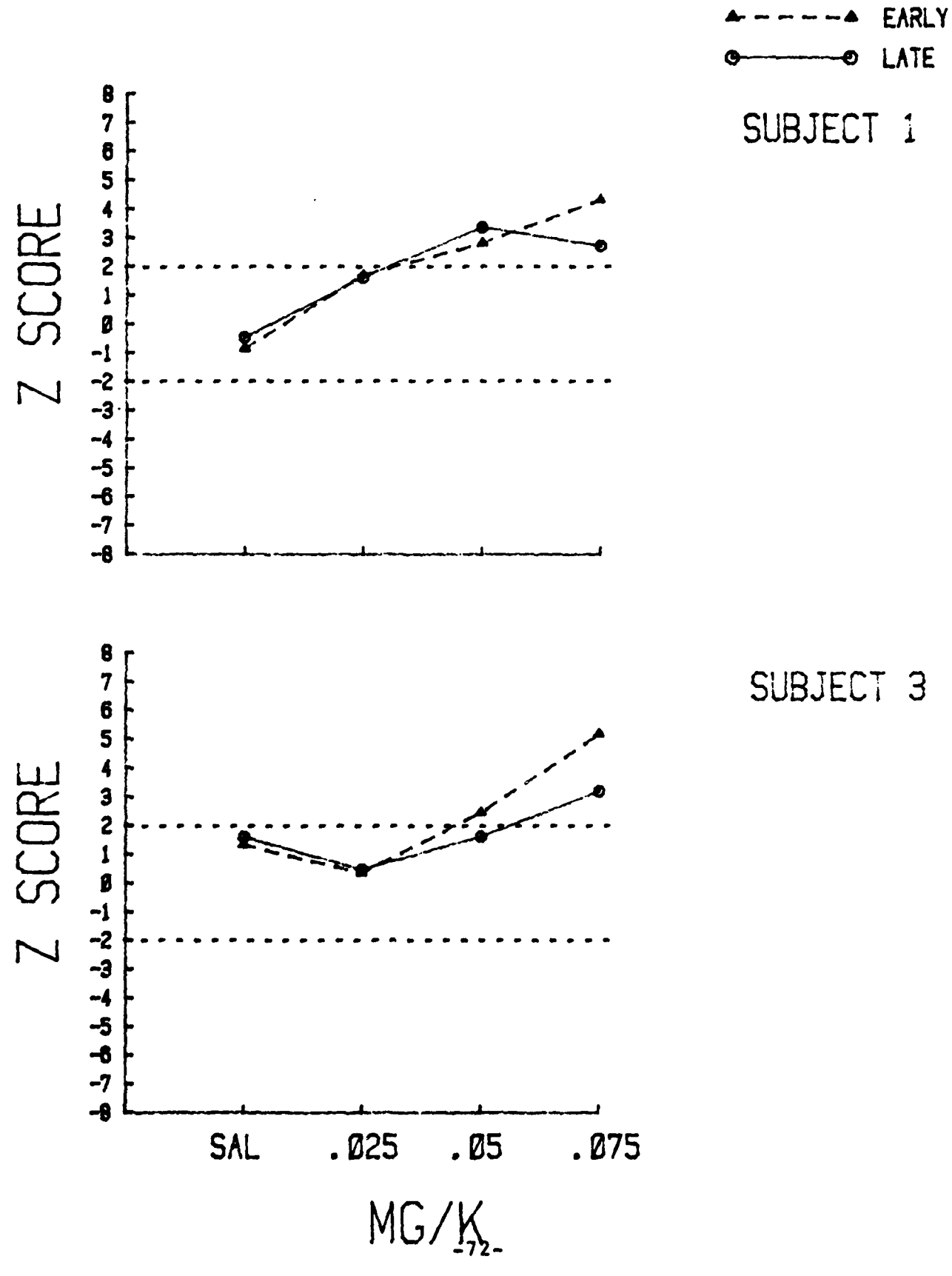

PHYSOSTIGMINE
NUMBER OF FIXATIONS TO FIND TARGET
EARLY
LATE
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
.025
.050
.075
MG/K

Figure 16


PHYSOSTIGMINE
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 1
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-12
(-11.01)
(-28.05)
SUBJECT 3
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-11
(-10.12)
(-39.67)
(-21.29)
SAL
.025
.05
.075
MG/K

PHYSOSTIGMINE
TIME TO FIND TARGET



PHYSOSTIGMINE
NUMBER OF FIXATIONS TO FIND TARGET

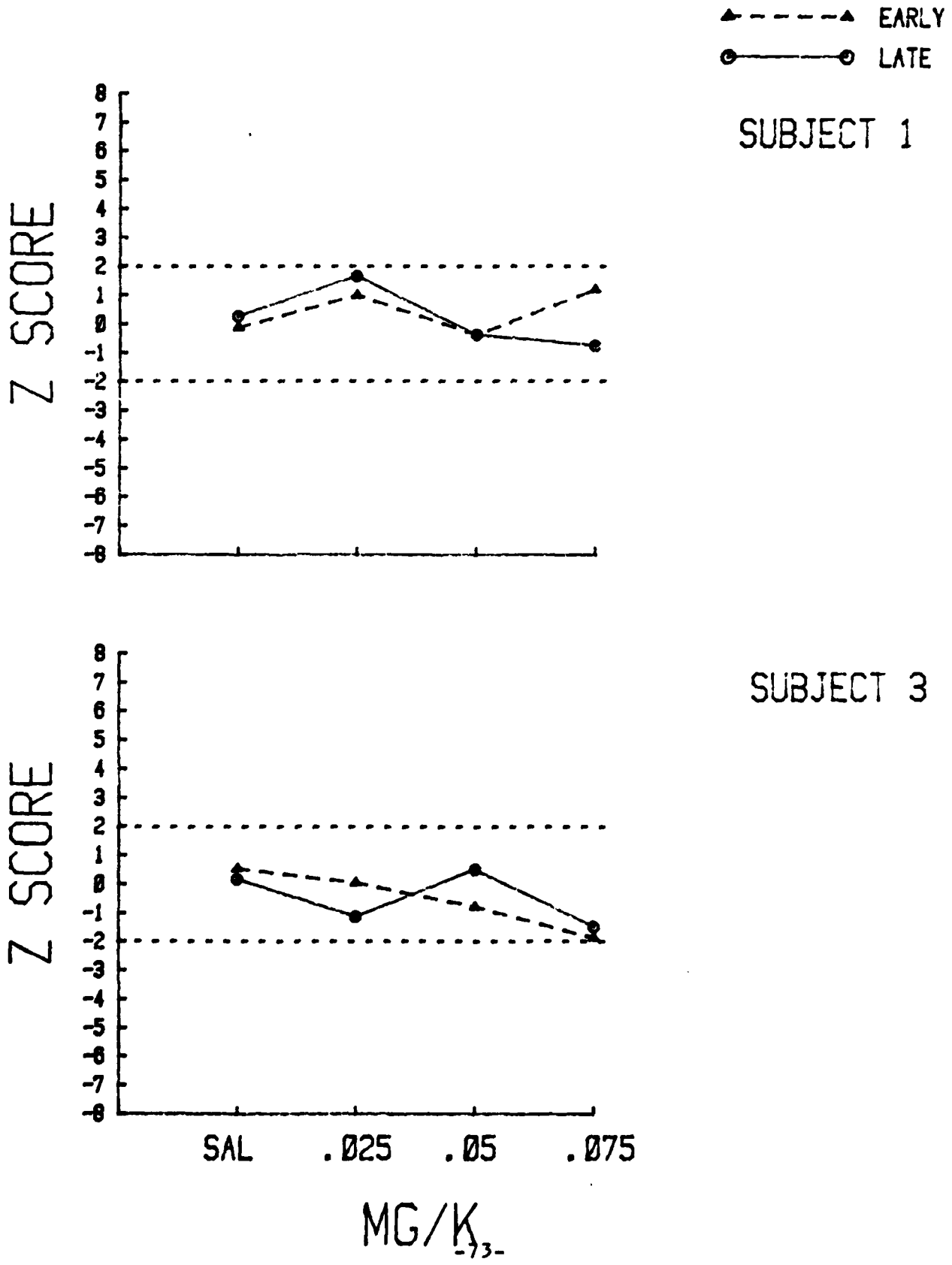


Table 11. Physostigmine

"Worst Case" Absolute Scores
Subject 3
Dose: .075 mg/K

	Baseline	Drug/Early	Drug/Late
Percent of targets fixated	98.3 ±1.8	16.7	20.37
ON SUCCESSFUL TRIALS:			
Reaction time to begin search (msec):	243 ±19	156	372.6
Time required to fixate target (msec)	490 ±51	697	705.7
Number of fixations required to fixate target	1.9 ±.16	1.59	1.69
Length of scan path to fixate target (radian distance in degrees of visual angle)	24.6 ±2.9	23.7	23.1
Saccade duration (msec)	35.2 ±2.8	123.1	50.5
Velocity of searching saccades (radian distance/sec; in degrees)	329 ±13.9	253.7	281.4

TAB

Table 12. Schedule of Completed Drug Trials

Doses (mg/K):		TMB_4	Atropine	Benactyzine
	A =	.57	.014	.057
	B =	1.82	.045	.182
	C =	5.7	.14	.57

Subject 1	A	B	B	D	C	C		
	c	c	c	c	c	c		
Subject 3	B	A	C	B	C	D		
	c	c	c	c	c	c		
Subject 4	D	C	B	B	A	D	A	C
	c	c	c	c	c	c	c	c
Subject 5	C	A	A	D	C	B	B	
	c	c	c	c	c	c	c	

TAB A = .57/.014/.057 mg/K

Neurological Symptoms: Mydriasis appeared in 3 or 4 subjects. A slight tremor occurred for a few minutes in one monkey but this single observation was not repeated at any other dose level.

Oculomotor Competence: Two of the subjects' records (1, 3) showed spiking transients in the vertical channel. The record and calculated parameters were otherwise normal.

Visual Search: Testing proceeded normally for the most part. Two subjects(3, 5) paused occasionally during the Early session but their Search performance was competent.

TAB B = 1.82/.045/.182

Neurological Symptoms: Moderate mydriasis in both sessions, but no other symptoms.

Oculomotor Competence: Spikes, drifting fixations, and small step-wise saccades appeared in the record. These shortened the average fixation duration (255 vs. 417 ± 46) and increased average drift (50 vs. 38 ± 4.4 min.). The step-wise saccades also registered as an undershoot of the target (targeting error: 52 w. 32 ± 4 min.). Oculomotor parameters returned to normal during the Late session.

Visual Search: The B dose occasionally halted testing but only one subject (3) was severely disrupted and only during the Early session. However, this dose produced performance decrements in two other monkeys (3, 4), and caused a real but lesser decrement in subjects 1 and 5.

TAB C = 5.7/.14/57

Neurological Symptoms: Moderate mydriasis was present in all subjects. Muscle weakness was evident in only one animal.

Oculomotor Competence: The records are characterized by ragged, drifting fixations, spikes, 4 small step-wise saccades. Eye movements were more ataxic during periods when the monkey was not actively searching for targets. Fixations were shortened on the average (284 vs. 565 ± 39 msec) and had excessive drift (47 vs. 28.2 ± 2.8 min.). Saccadic velocity was slowed (176 vs. 267 ± 24 deg/sec.). During the Early period all monkeys were similarly affected. During the Late session the oculomotor parameters of Subjects 1 & 5 returned to normal.

Visual Search: Two subjects (3, 4) stopped testing altogether and their data are taken from trials triggered by us. The other two paused intermittently. Reaction time to begin search remained normal but the graphs reveal consistent decrements in all other formal measures during the Early session. Late session performance improved considerably.

In summary, the effects of TAB had elements of the effects seen previously with its component drugs. The early disruption of testing was reminiscent of benactyzine, the Search decrements at higher doses like that of atropine, and the oculomotor dysmetria similar to that of TMB_4. However, there were differences. The performance decrements did not

persist as long and there was less mydriasis, less overt muscle weakness than we had previously seen with atropine.

Relationship Between Drug Effects and Task Complexity.

Three levels of test difficulty were originally created to see if the degree of performance decrement from drugs might depend on the difficulty of the task. In practice there was a difference in difficulty at least between the No and the High Noise conditions. During baseline days the monkeys required an extra 200 msec. on the average to find the target on the High Noise condition. However, this difference may not have been sufficient to tease out a drug-task difficulty interaction if one occurred. Our impression in reviewing the data informally was that drugs affected the Noise conditions evenly. The last graphs show Z scores of TAB's effect in the Early session, separated for the No and High Noise conditions. There is no consistent trend for one Noise condition to be affected more than the other. This confirmed our informal impression and discouraged us from carrying out a formal test of a drug-task difficulty interaction.

OCULOMOTOR RECORD - TAB

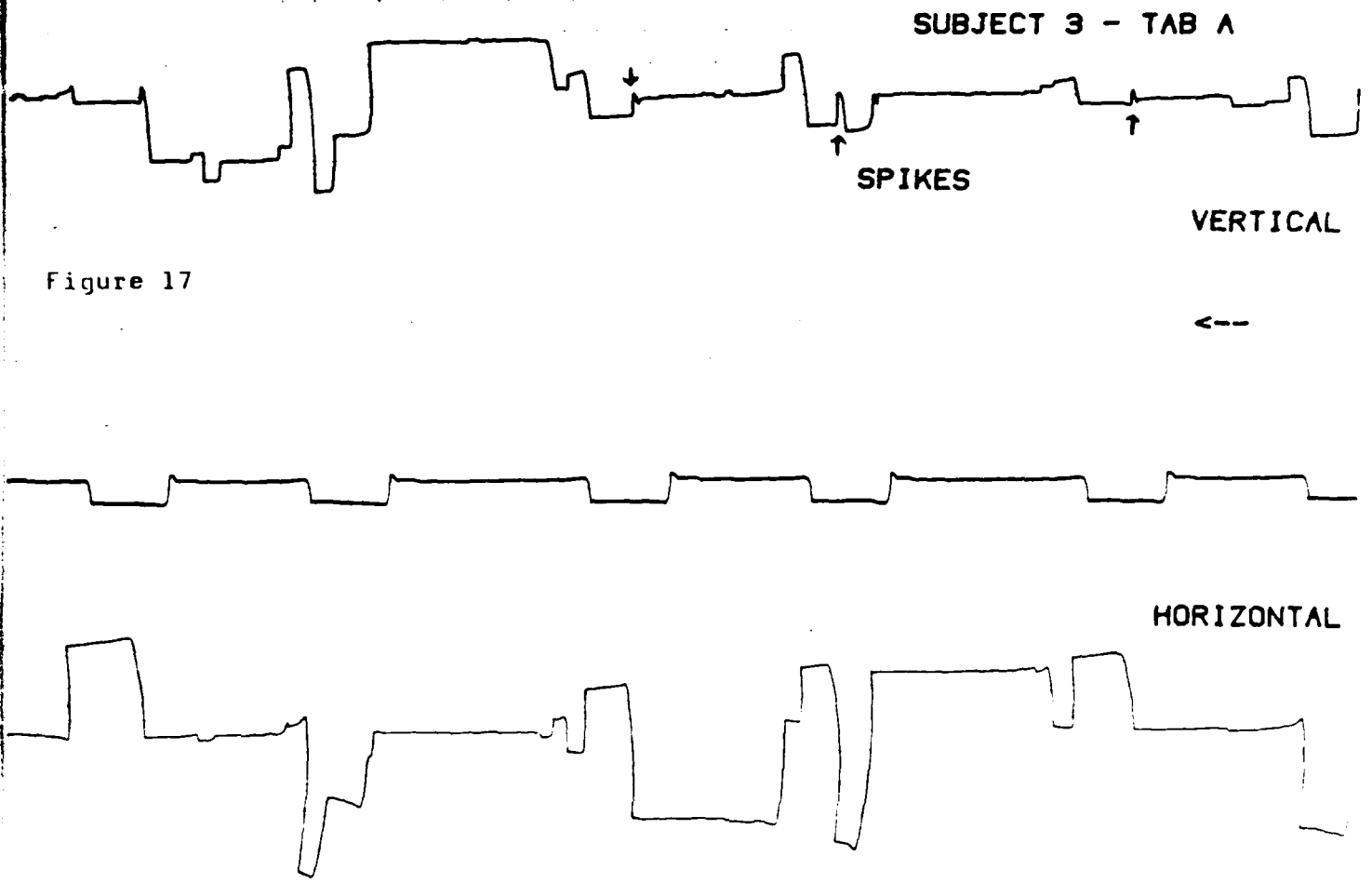
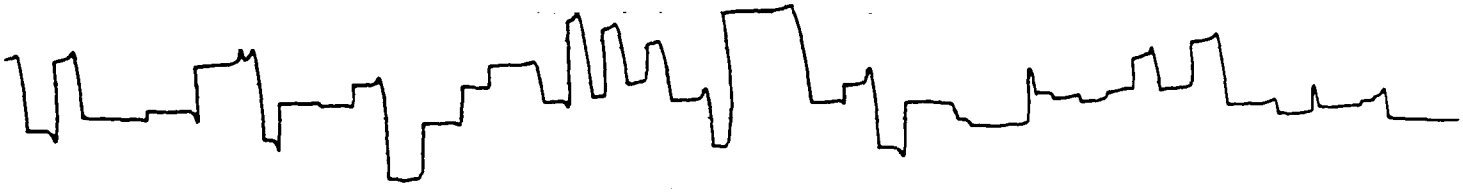
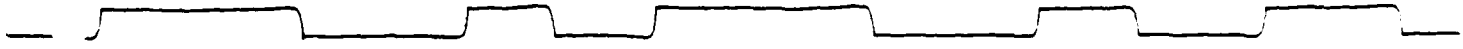


Figure 17

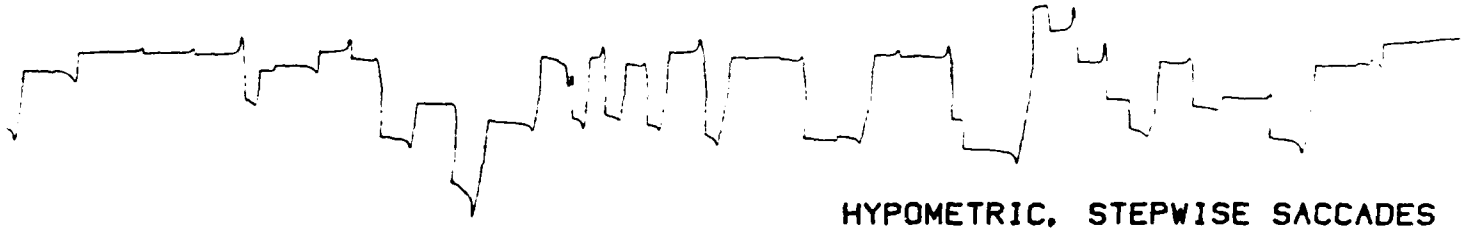
SUBJECT 3 - TAB C



VERTICAL

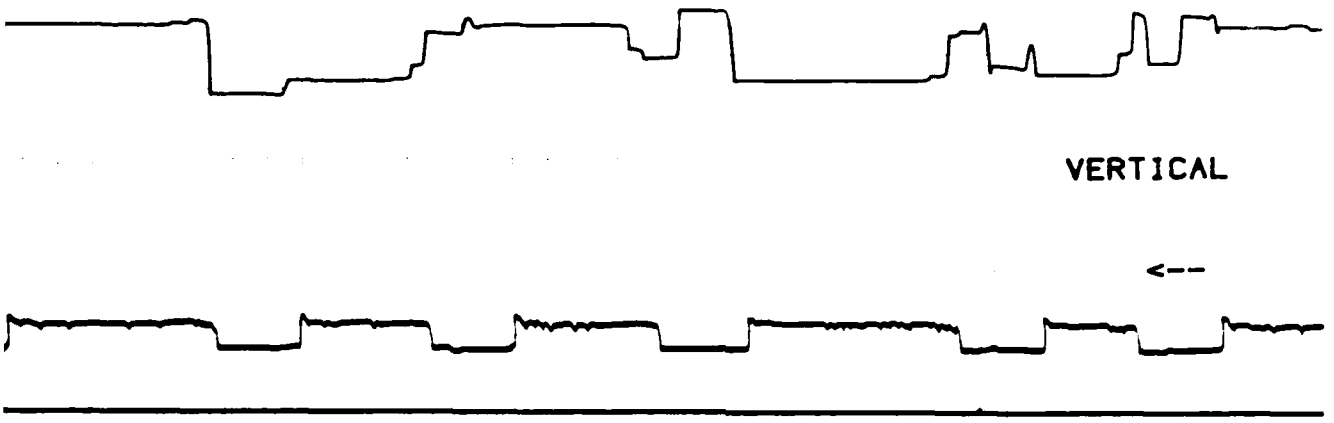


HORIZONTAL



HYPOMETRIC, STEPWISE SACCADES

SUBJECT 4 - TAB A



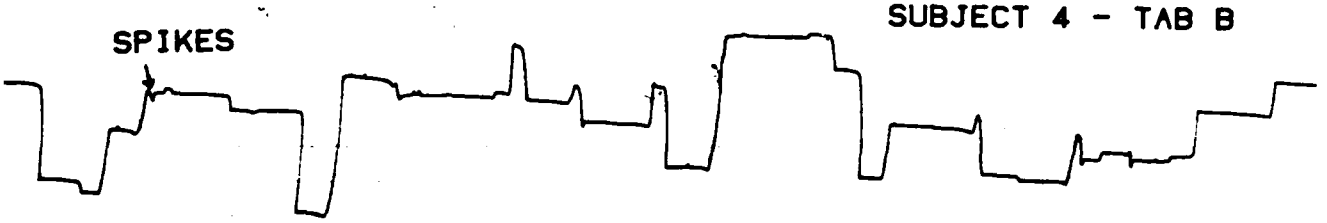
VERTICAL

<--

HORIZONTAL

SUBJECT 4 - TAB B

SPIKES



VERTICAL

HORIZONTAL

SUBJECT 4 - TAB C

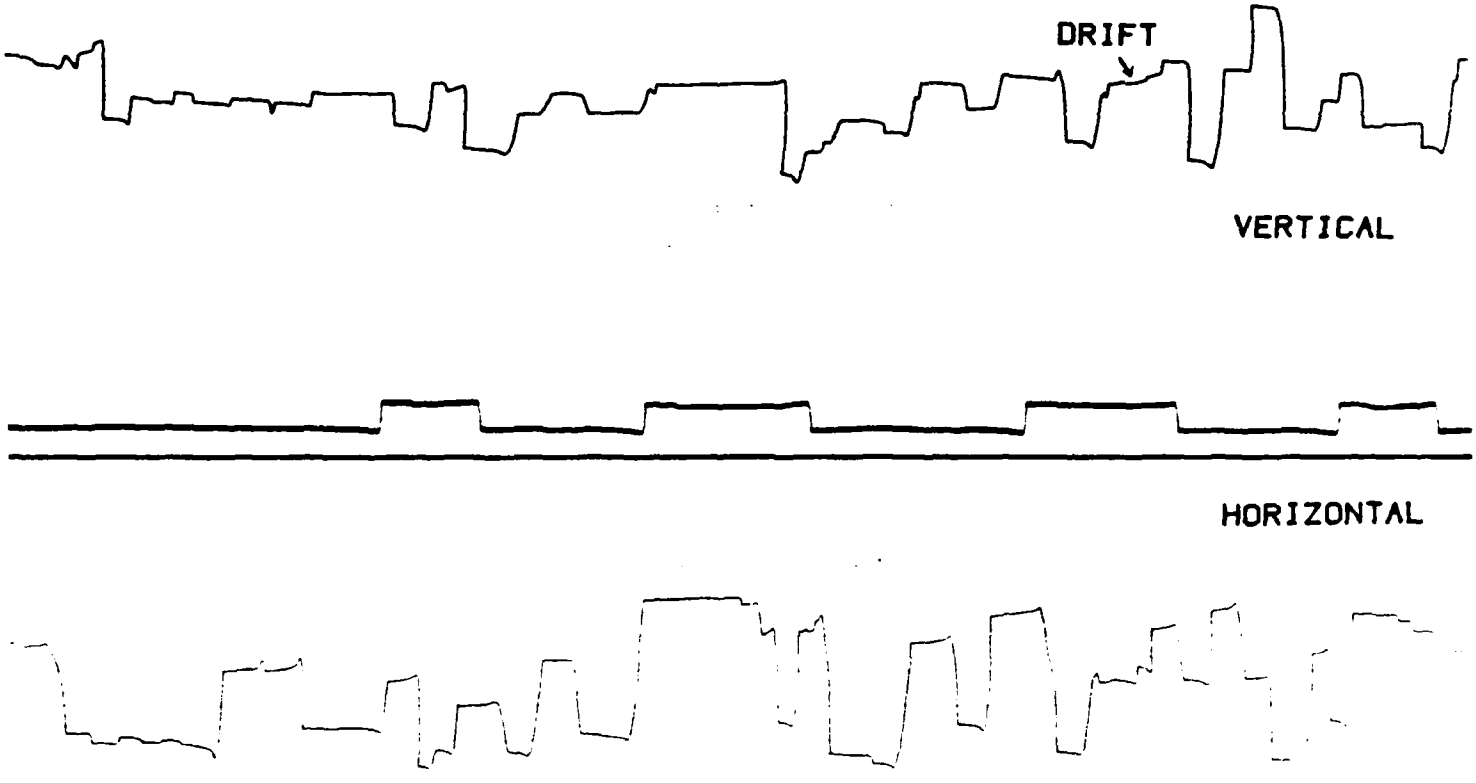
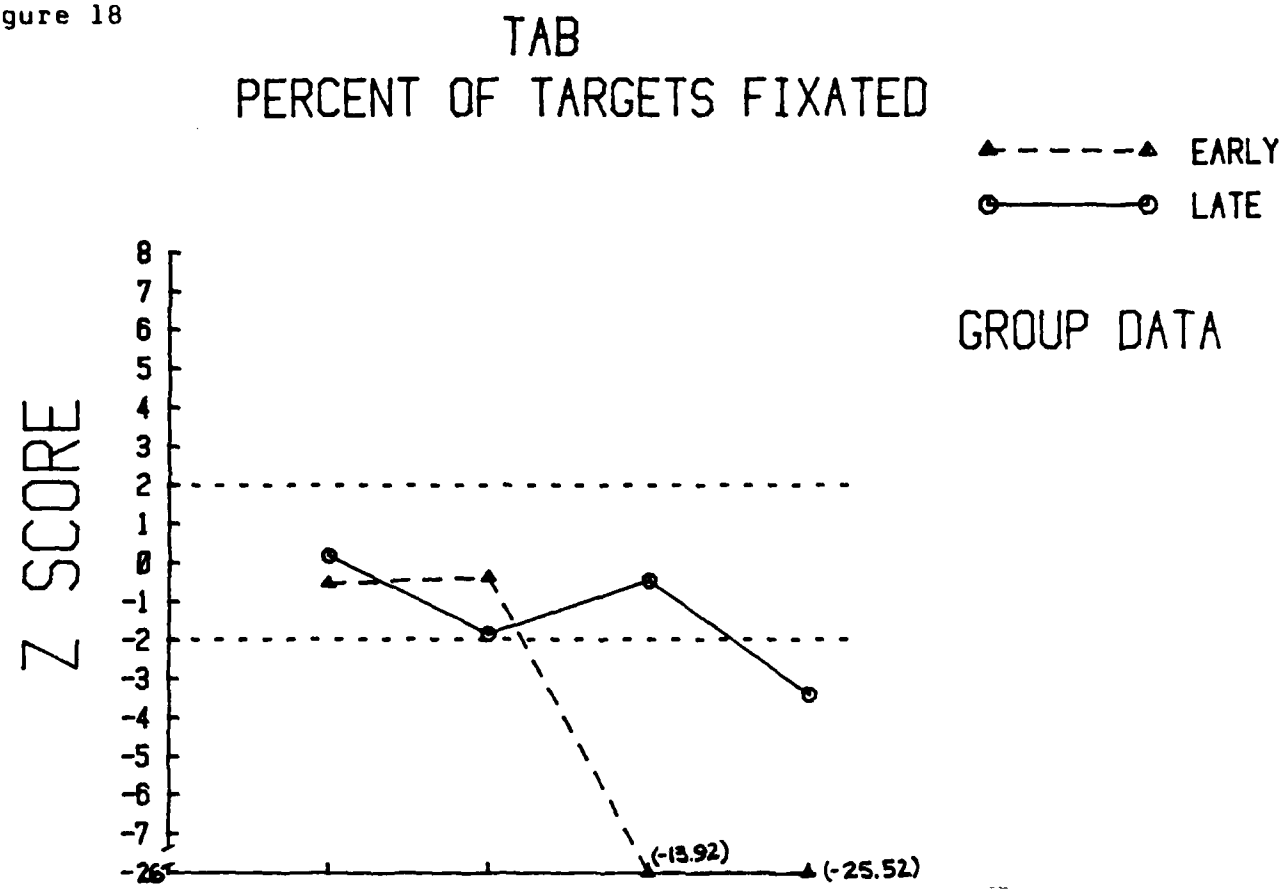
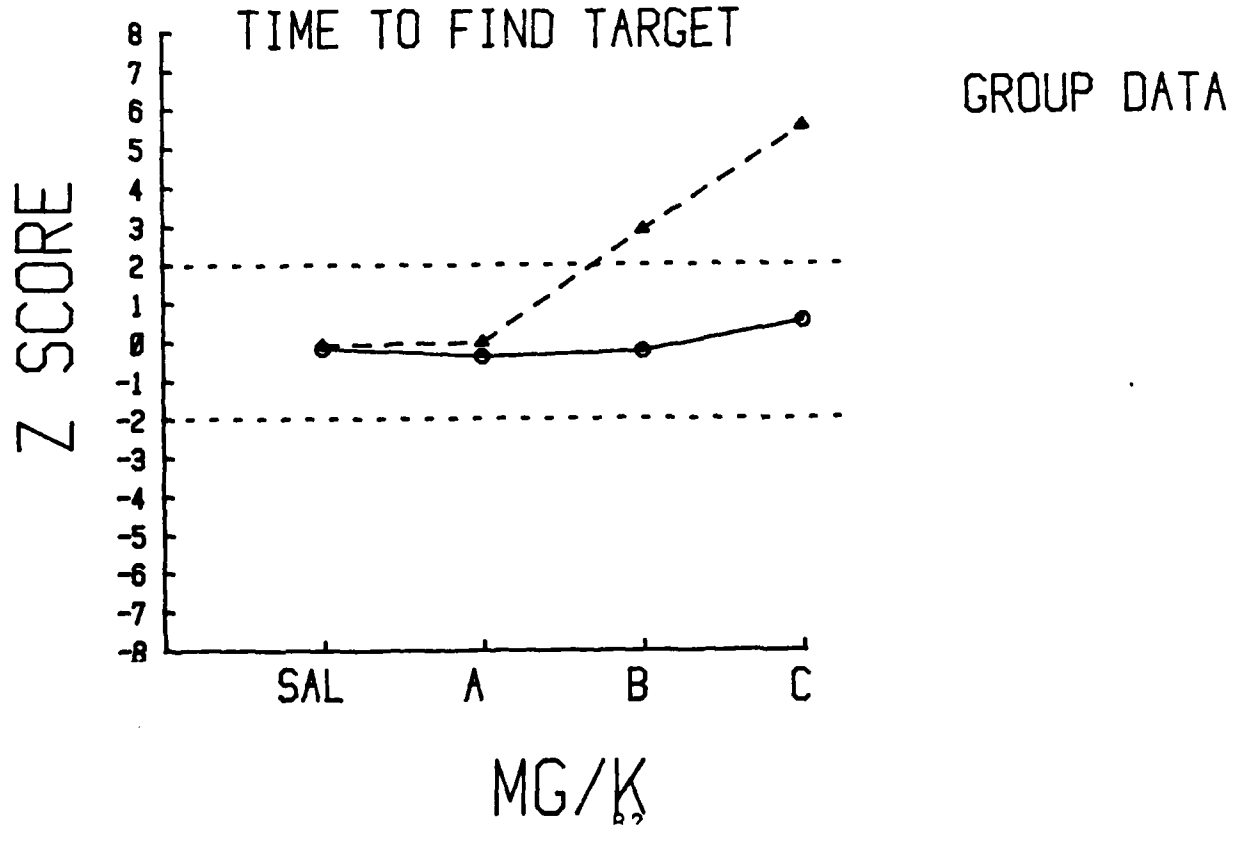


Figure 18


TAB
PERCENT OF TARGETS FIXATED
EARLY
LATE
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-26
(-13.92)
(-25.52)


TIME TO FIND TARGET
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
A
B
C
MG/KG

TAB
NUMBER OF FIXATIONS TO FIND TARGET

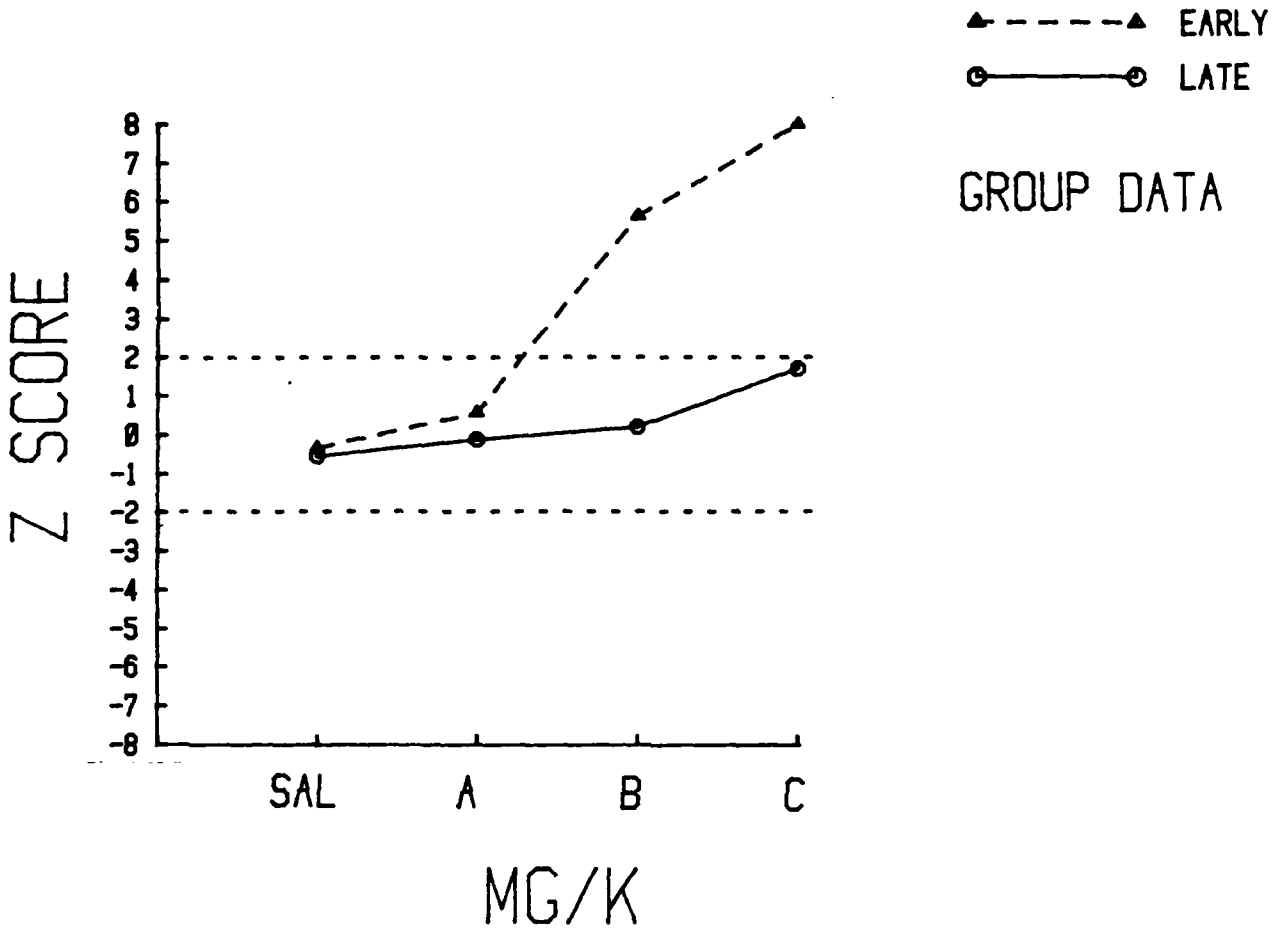
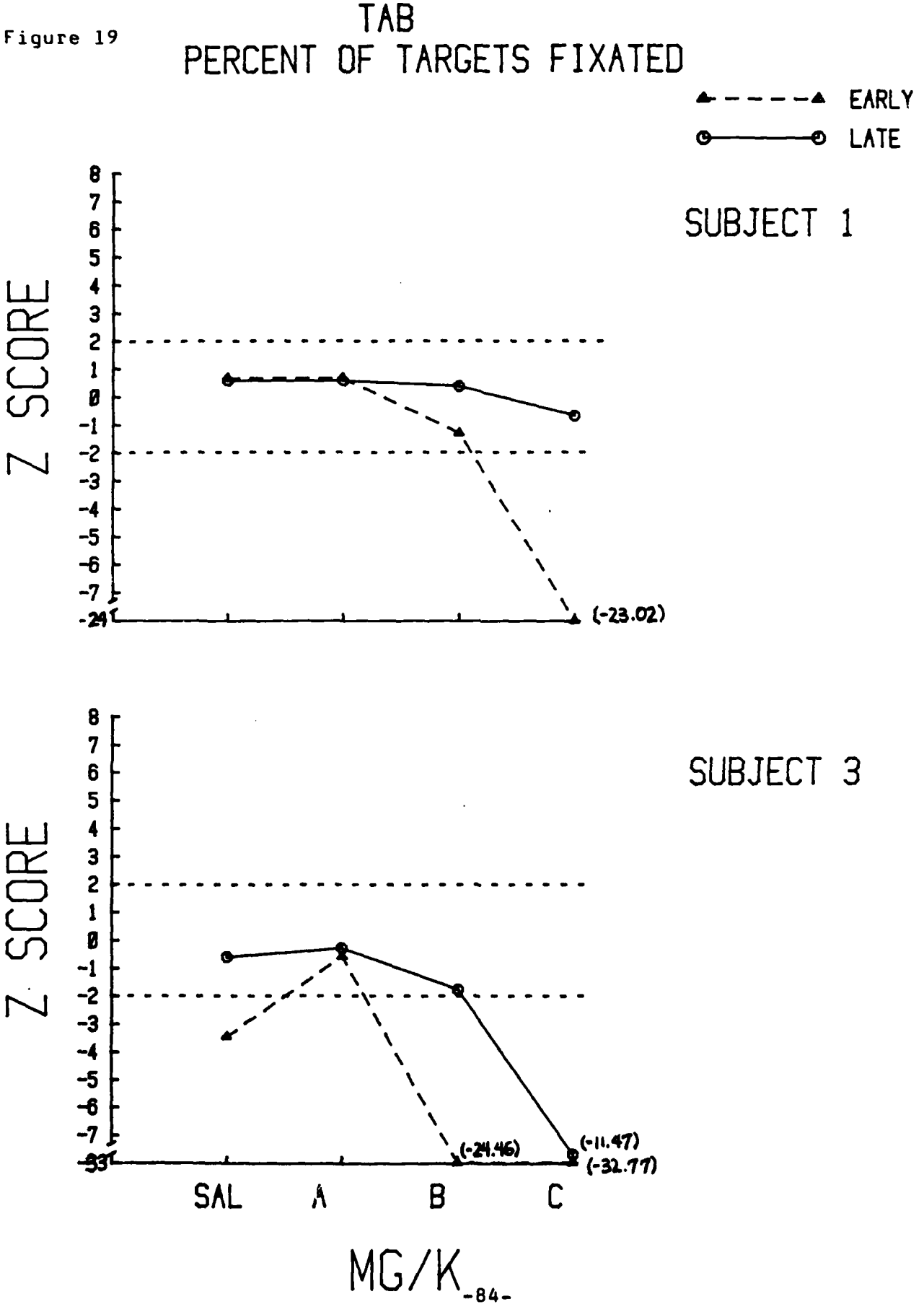
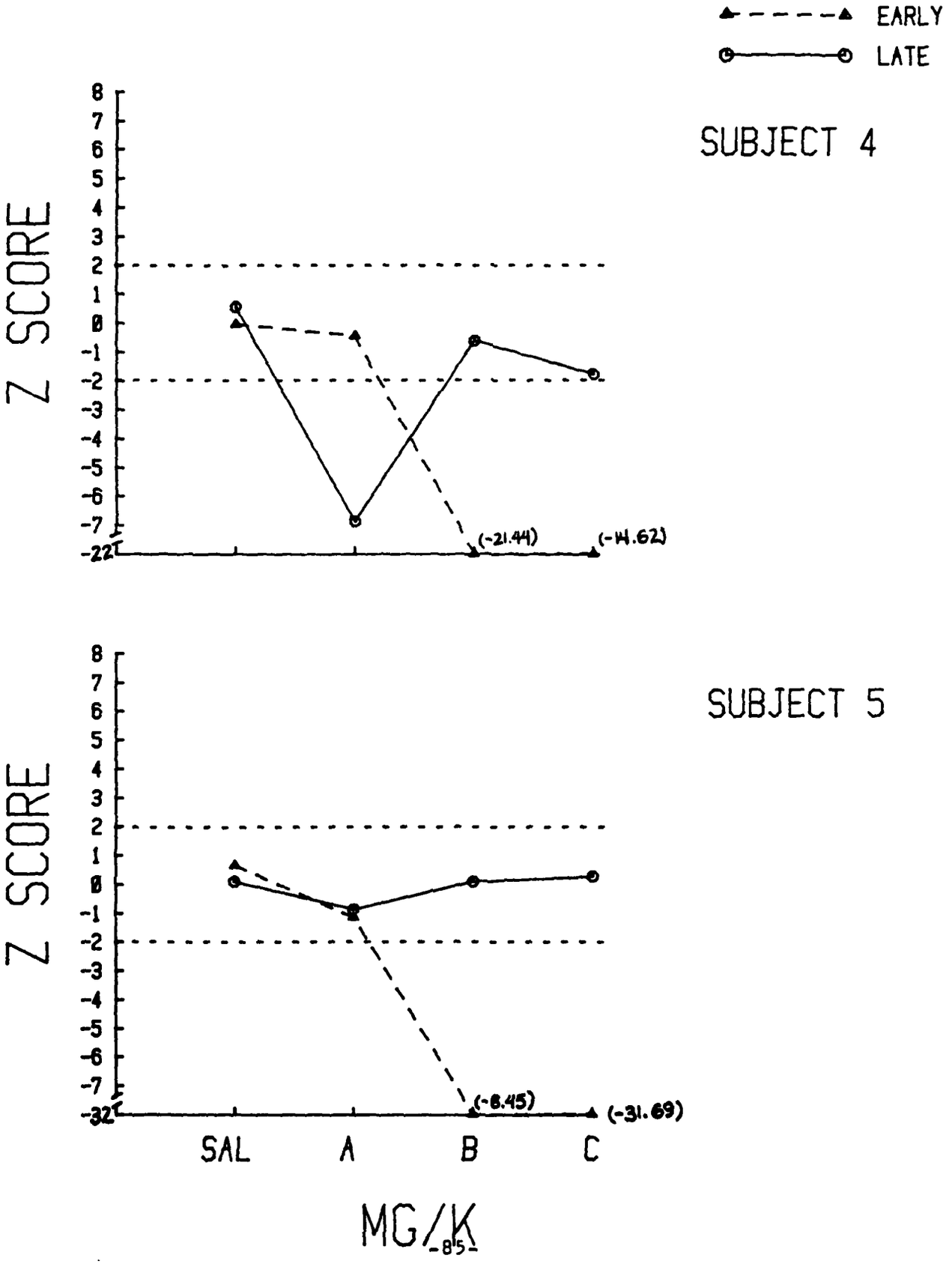


Figure 19

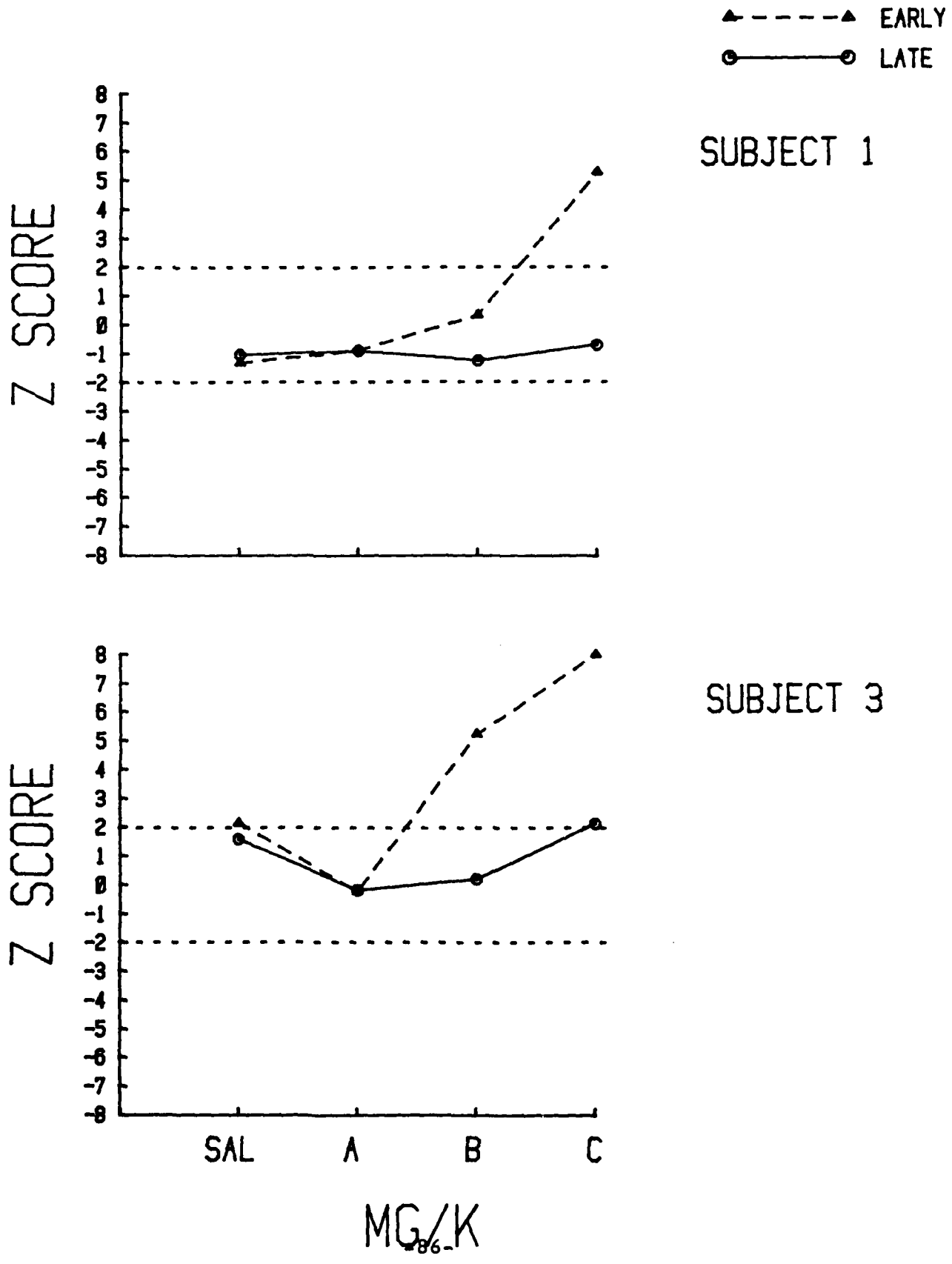

TAB
PERCENT OF TARGETS FIXATED
EARLY
LATE
SUBJECT 1
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-24
(-23.02)
SUBJECT 3
Z SCORE
-33
(-24.46)
(-11.47)
(-32.77)
SAL
A
B
C
MG/K

TAB

PERCENT OF TARGETS FIXATED

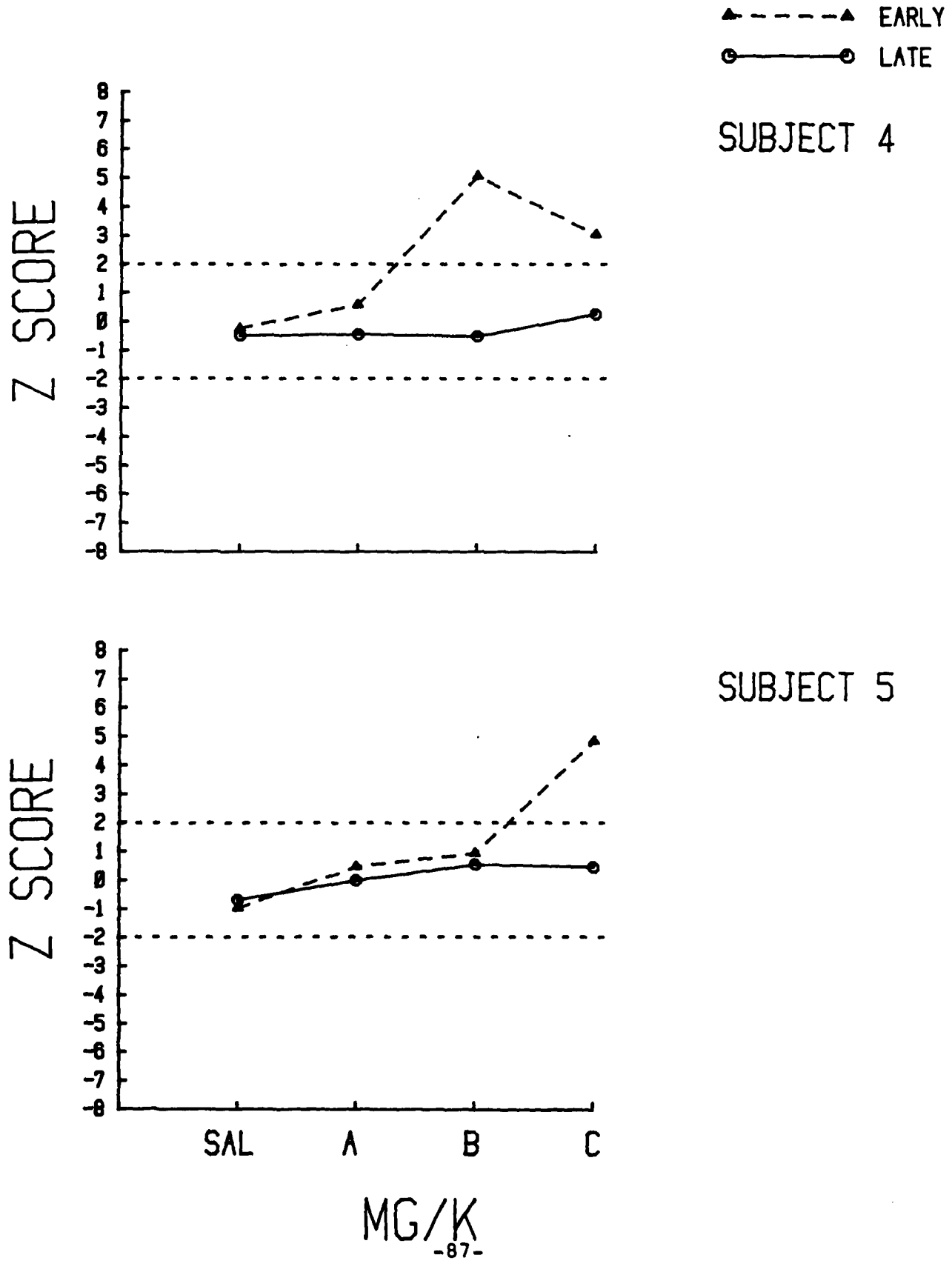


TAB
TIME TO FIND TARGET



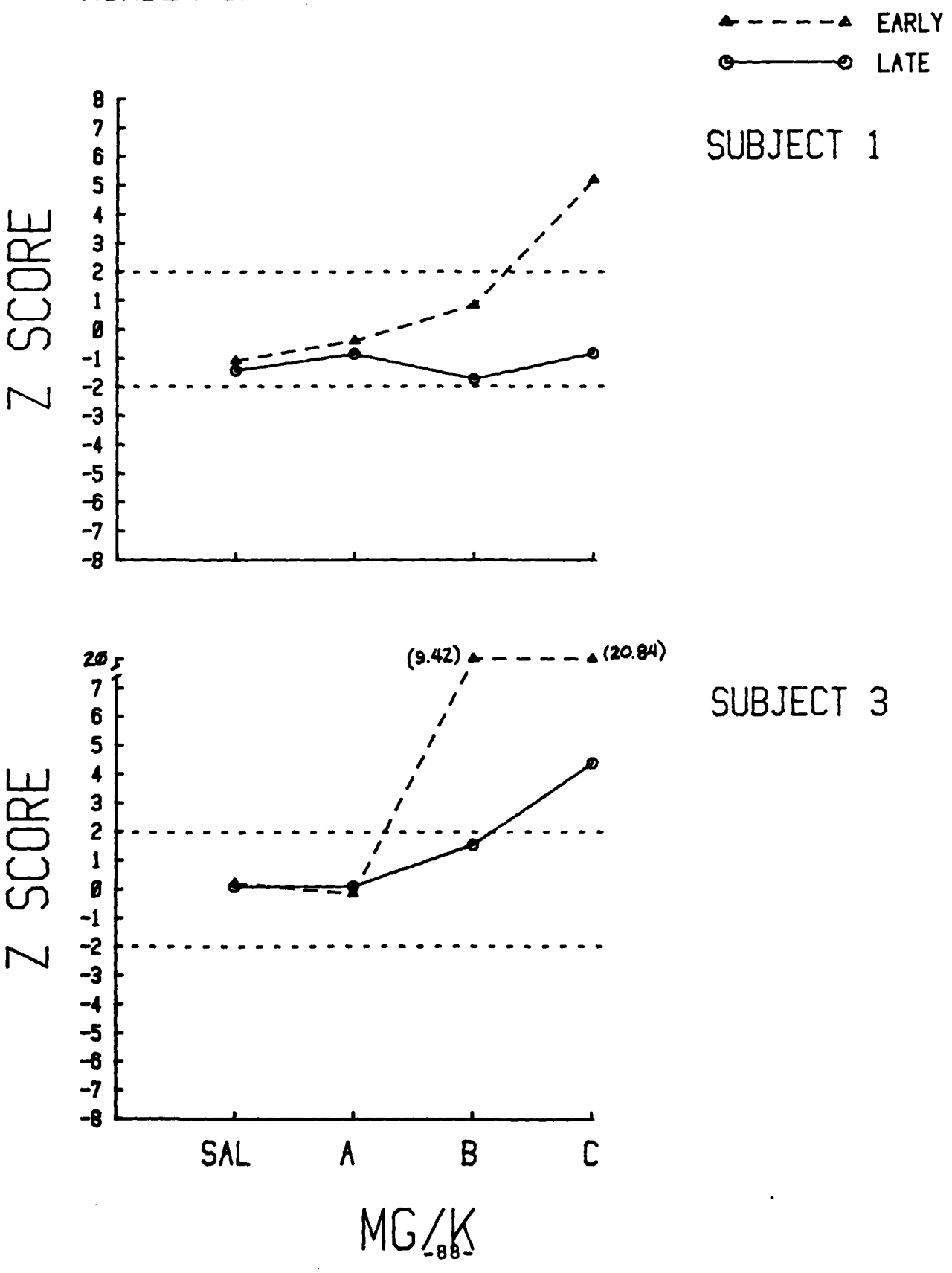
TAB

TIME TO FIND TARGET



TAB

NUMBER OF FIXATIONS TO FIND TARGET



TAB

NUMBER OF FIXATIONS TO FIND TARGET

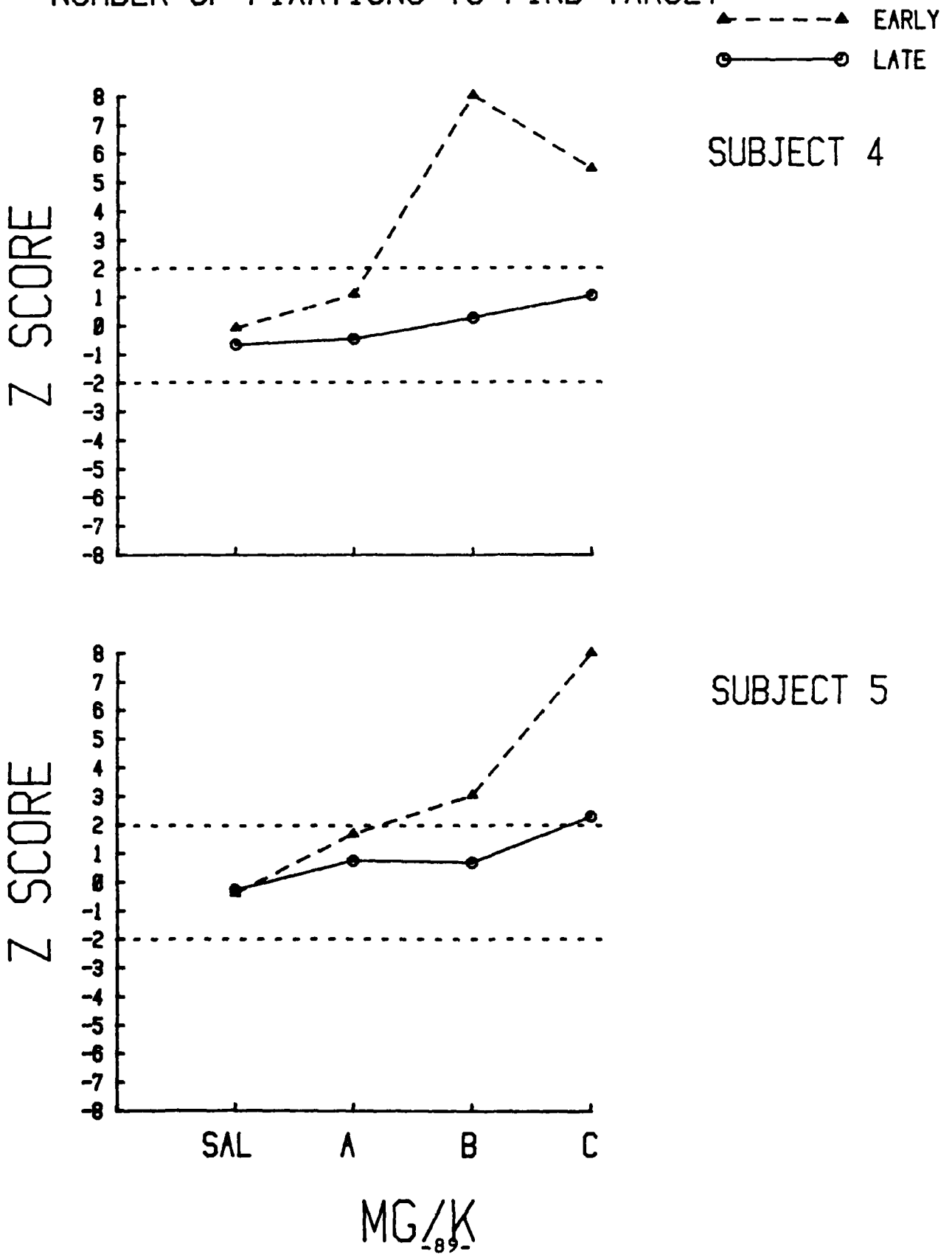
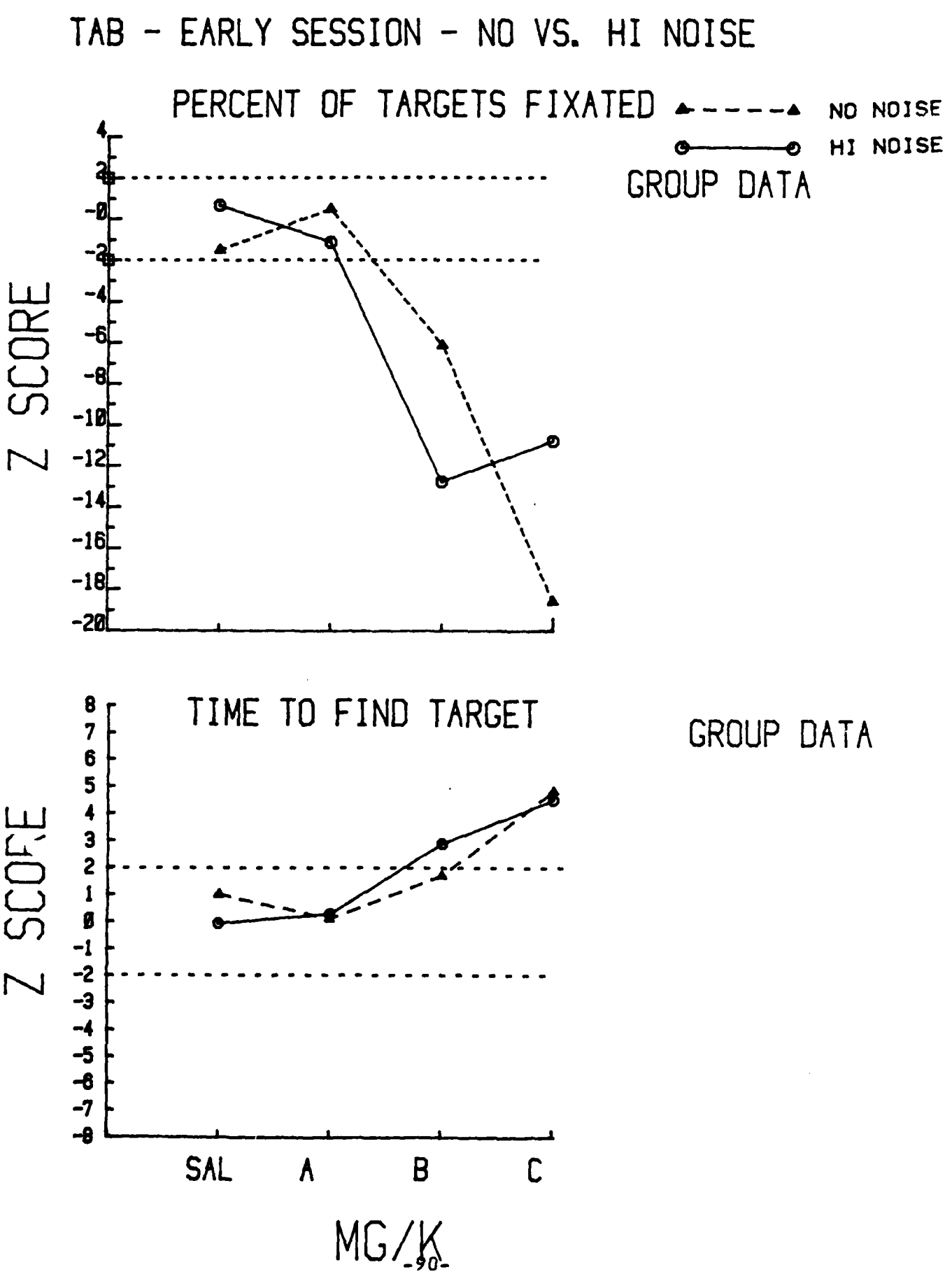


Figure 20


TAB - EARLY SESSION - NO VS. HI NOISE
PERCENT OF TARGETS FIXATED
NO NOISE
HI NOISE
GROUP DATA
Z SCORE
4
2
-0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
TIME TO FIND TARGET
GROUP DATA
Z SCORE
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
SAL
A
B
C
MG/K

TAB - EARLY SESSION - NO VS. HI NOISE

NUMBER OF FIXATIONS TO FIND TARGET

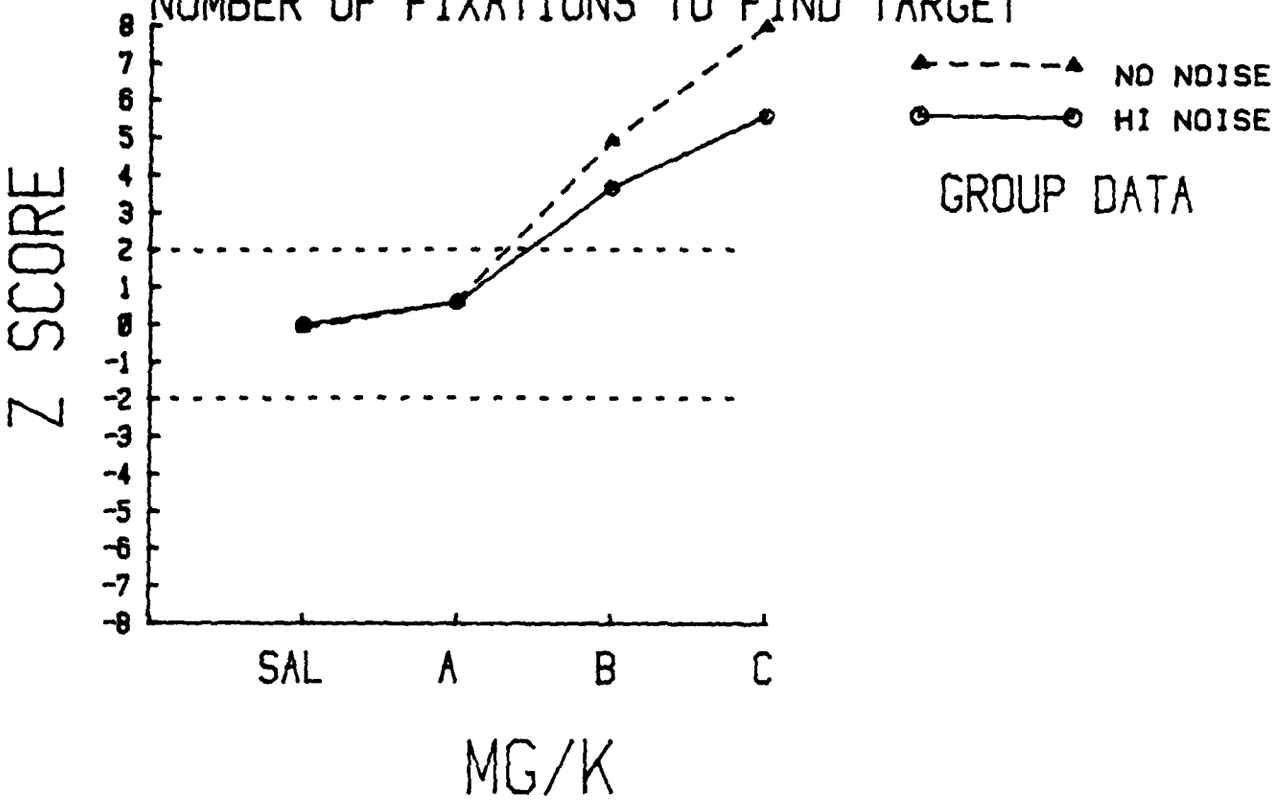


Table 13. TAB

"Worst Case" Absolute Scores
Subject 3
Dose C (TMB_4 = 5.7; Atropine = .14; Benactyzine = .57)

	Baseline	Drug/Early	Drug/Late
Percent of targets fixated:	99.2 ±2.3	24.0	32
ON SUCCESSFUL TRIALS:			
Reaction time to begin Search (msec.)	281 ±38	237	328
Time required to fixate target (msec.)	369 ±54	855	567.8
Number of fixations required to find target	1.19±.09	3.0	1.50
Length of scan path to fixate target (radian distance in degrees of visual angle)	12.2 ±2.5	23.3	11.1
Saccade duration	24.4 ±4.9	53.6	51.1
Velocity of searching saccades (distance/sec., in degrees)	267 ±235	176	231

Report Summary

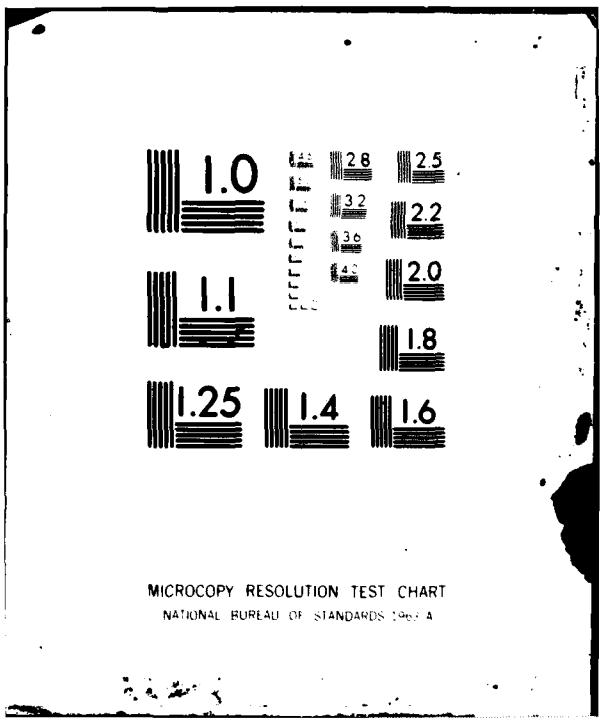
The dosages tested in this protocol represent the low range of toxicity of these cholinospecific agents. The animals' lives were never threatened during any of the trials. They experienced no obvious respiratory stress and were never so weakened as to prevent postural support. Vomiting occurred with only one agent and then in only one subject. Weekly exposure to the drugs for over a year did not affect the monkeys' high level of baseline performance. The lowest doses of TAB or its components had no or only subtle effects. Vision and eye movements remained competent and visual search was conducted with normal efficiency and very little interruption. Physostigmine at the lowest dose halted testing intermittently but had no other effect.

The protocol tested an adequate range of ascent from these lower dosages. In all cases the highest doses tested caused sufficient decrements to suggest that the effect of further dosage increases on these measures of performance would be uninformative.

As the doses increased some symptoms appeared which were common to all the drugs. The highest doses caused some unwillingness of the monkeys to initiate testing trials. The effect was variable. Benactyzine and physostigmine disrupted testing most completely. With TMB_4 the monkeys though rendered incompetent by the drug nonetheless tended to persevere at testing. This unwillingness to test was interpreted as a motivational problem when it occurred together with good searching performance on trials initiated by the experimenter. In addition to this unwillingness to test at higher doses, all of the drugs introduced some degree of ataxia into their eye movements. Each agent lent its own signature to the oculomotor trace but with all the drugs it was common for the monkey to be unable to hold a fixation point (drift). The records also frequently contained a larger number of spiking transients than was normal. Except for the motivational problem mentioned above, most or all of the deficits described in this report could be subsumed under the rubric "oculomotor." Tardy initiation of eye movements, slowed and hypometric saccades requiring corrective adjustments could ac[illegible] for most of the delayed fixations of targets or failure to find t[illegible] before the end of the trial. There was no strong evidence for [illegible] visual or cognitive decrement that was independent of oculom[illegible] problems. Visual or cognitive problems may occur with these [illegible] but here they were overshadowed by the oculomotor proble[illegible] were obvious in the oculomotor records and which I believe [illegible] for the abnormal performance scores in visual search.

The protocol included 3 classes of agents: anti[illegible] (atropine, benactyzine), the anticholinesterase [illegible] a cholinesterase reactivator (TMB_4). No swee[illegible] the brand of toxicity caused by each class [illegible] ences were noticed between classes. For e[illegible] ergics caused mydriasis and more muscle w[illegible]

AD-A117 391 STATE UNIV OF NEW YORK AT ALBANY RESEARCH FOUNDATION F/G 6/15
ASSESSMENT OF NEUROLOGICAL EFFECTS OF DRUGS ON OCULOMOTOR AND V--ETC(U)
FEB 82 E G KEATING DAAK11-79-C-0027
UNCLASSIFIED NL


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS

agents. Slow meandering pursuit-like eye movements were also peculiar to these two drugs. However, these two drugs of the same class also differed from each other in the type and time course of their effects. Atropine had a delayed, accumulating effect on performance. Benactyzine interfered with the monkeys' willingness to test for 15-38 minutes but had minor other effects on performance. Similarities in toxic effects often crossed class boundaries. The anticholinergic benactyzine and the anticholinesterase physostigmine were most similar in their tendency to disrupt testing. The symptom which at first appeared most confined to a single drug class was the peculiar shape of the oculomotor undershoot produced by TMB_4. Current research in our laboratory has found a similar though less severe symptom with the related drug pralidoxime. However, now a similar oculomotor record is showing up in cynomolgous monkeys given physostigmine so it, too, may not be confined to a single class of cholinergic action.

A last point is in regards to the effects of TAB. The symptoms it produced were reminiscent of the deficits seen with its component drugs. Search performance was disrupted, indicating no behaviorial tolerance to the effects of the drugs after more than a year's testing. However, the oculomotor and neurological symptoms, though like in kind, were less severe in degree with TAB than expected. Physiological compensation to cholinospecific agents appears unlikely given our once-weekly schedule of injections. The attenuated effects of TAB could be due to a counterbalancing of effects of 3 components whose cholinergic actions are to some extent antagonistic to each other.

References

Brimblecombe, R. W., Drug Actions on Cholinergic Systems, University Park Press, Baltimore, 1974.

Duffy, F. H., Burchfiel, J. L., Bartels, P. H., Gaon, M., and Sim, V. M., Long-term effects of an organophosphate upon the human electroencephalogram, Toxicology & Appl. Pharmacol. 47 (1979) 161-176.

Fuchs, A. F., & Robinson, D. A., A method for measuring horizontal & vertical eye movement chronically in the monkey, J. Appl. Physiol. 21 (1966) 1068-1070.

Levin, H. S. and Rodnitzky, R. L., Behavioral effects of organophosphate poisoning in man, Clinical Toxicology 9 (1976) 391-405.

Lipp, J., and Dola, T., Comparison of the efficacy of HS-6 versus HI-6 when combined with atropine, pyridostigmine and clonazepam for soman poisoning in the monkey, Arch. Int. Pharmacodyn (in press).

Longo, V. G., Behavioral and electroencephalographic effects of atropine and related compounds, Pharmacological Review 18 (1966) 965-996.

Sidell, F. R. and Groff, W. A., Intramuscular and intravenous administration of small doses of 2-pyridinium aldoxime metho-chloride to man, J. of Pharm. Science, 60 (1971) 1224-1228.

APPENDIX

Algorithm for Computer Analysis of Eye Movements

The rotation of the animal's eye coil induced a change in voltage that was separated into its horizontal and vertical components by a phase detector/amplifier. The amplifier sent a continuous analog signal over horizontal and vertical channels to a PDP 1103 microprocessor which sampled each channel every millisecond. The first task was to separate fixations from saccadic movements of the eyes, the second to plot the location of the fixations in reference to the monkeys' point of regard on the projection screen.

In separating saccades and fixations, the computer tentatively judged to be a saccade any change in position of the eye from one sample to the next that exceeded 10^{0}/sec. (in radial degrees of visual arc). This always occurs during true saccades but may also happen spuriously during fixations and represents both electronic noise and some physiological tremor of the ocular muscles. Therefore, a smoothing criterion was imposed. An epoch was finally judged a saccade only if 4 successive samples exceeded the velocity criterion. Once a saccade was named the computer declared the end of the previous fixation and used the last sample of the fixation to plot its position. A saccade was terminated similarly. When the velocity dropped below 10^{0}/sec and remained below for 100 successive samples, a fixation was declared and its beginning set at the first sample that met criterion. These criteria were set empirically from examining by eye dozens of eye records and deciding arbitrarily what portions looked like saccades or fixations. The computer's velocity and smoothing criteria were adjusted until it matched our decisions. The present criteria correctly name all shifts of gaze that are greater than 0.5^{0} of visual arc.

The second task of locating the fixations in reference to the viewing screen was accomplished during a calibration period at the start of testing. The monkey fixated a target placed at the center of the screen, then the left hand,then bottom boundary of the viewing area. This provided boundary reference voltages to the computer which allowed it to position subsequent fixations, within the defined space.